PART I. SYNTHESIS OF NEW BARBITURIC ACID DERIVATIVES

PART II. SYNTHESIS OF NEW GLUTAMINE AND AMINOGLUTARIMIDE DERIVATIVES

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Date approved by Chairman:_____

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SUMMARY

PART I

The object of this research was to prepare certain barbituric acid derivatives containing an alkyl substituent and a sulfanilamido or an N-acetylsulfanilamido group at their 5-positions. Due to reports of synergism of "sulfa" drugs with barbiturates, it was felt that such compounds may have therapeutic value. The 5,5-disubstituted barbituric acids which were produced are similar to 5,5-dialkyl-barbituric acids, a class of compounds known to possess pronounced hypnotic activity. All of the compounds eventually prepared also contained an alkyl substituent on the sulfonamide nitrogen.

In early attempts to prepare such a compound, 5-ethyl-5-sulfanilamidobarbituric acid, N-acetylsulfanilyl chloride was allowed to react with 5-ethyluramil in either pyridine or aqueous trimethylamine. In all cases the desired reaction failed to occur. Unchanged 5-ethyluramil was recovered after many of these reactions. One problem associated with this approach was the lack of an inert mutual solvent for both of the reactants.

A second approach was to effect a condensation of diethyl N-acetylsulfanilamidomalonate and urea in the presence of potassium t-butoxide. The former compound was prepared by the condensation of N-acetylsulfanilyl chloride and diethyl aminomalonate hydrochloride in pyridine. However, the sulfonamide was destroyed under the reaction

conditions and none of the desired product was obtained. One product which was isolated from this reaction mixture was uramil, but it is not completely clear how this compound was formed.

The successful synthesis of sulfanilamidobarbituric acids was finally accomplished by modifying the 5-alkyluramils originally investigated. It was found that 5,7-dialkyluramils reacted readily with sulfonyl chlorides to give the corresponding sulfonyluramils. The sulfonyl chlorides used for this reaction were p-nitrobenzene-sulfonyl chloride and N-acetylsulfanilyl chloride. When the latter sulfonyl chloride was employed, the resulting N-acetylsulfanilyluramil derivative could be converted to the free amine by selective hydrolysis of the acetyl group in refluxing dilute aqueous hydrochloric acid. The synthesis of 5-phenyl-7-sulfanilyluramils was accomplished by this method.

The exact reason for the reactivity of 5,7-dialkyluramils toward sulfonyl chlorides as opposed to the non-reactivity of the more simple 5-alkyluramils is not completely certain. The IR spectra of the former contain sharper absorptions in the carbonyl region than do the 5-alkyluramils. Such an observation may be due to the fact that certain enolic or zwitterionic forms are possible for 5-alkyluramils which are not possible in 5,7-dialkyluramils.

The sulfanilamidobarbituric acids prepared in the course of this work are being submitted for physiological evaluation.

PART II

The purpose of this research was to prepare certain glutamine derivatives, β-glutamine derivatives, and aminoglutarimide derivatives. It was felt that these compounds may have therapeutic value in the treatment of virus-related diseases. Many of the compounds prepared were sulfanilamide derivatives and can be expected to have usefulness in treating diseases of bacterial or protozoal origin.

The first compounds synthesized were N^5-substituted derivatives of sulfanilylglutamine. These compounds were synthesized by reaction of carbobenzoxyglutamic anhydride with an amine, hydrogenolysis of the carbobenzoxy group, reaction of the resulting glutamine derivative with p-nitrobenzenesulfonyl chloride, and subsequent reduction of the nitro-group to give the sulfanilamide derivative. Using this procedure, N^5-benzyl sulfanilylglutamine and N^5-phenyl sulfanilylisoglutamine were prepared.

A series of N^5-substituted β-glutamine derivatives was prepared also. A method of preparing β-glutamic acid from diethyl acetonedicarboxylate was developed. The β-glutamic acid was converted to carbobenzoxy-β-glutamic acid. The carbobenzoxy derivative was reacted first with the acetic anhydride, then with an amine to give a carbobenzoxy-β-glutamine derivative. The substituted β-glutamine can be isolated after hydrogenolysis of the carbobenzoxy group. Using this procedure, N^5-benzyl and N^5-propyl β-glutamine were prepared. The synthesis of sulfanilyl β-glutamic acid was effected from p-nitrobenzenesulfonyl-β-glutamic acid.

A series of β-carbobenzoxyaminoglutarimides was prepared by cyclization of the corresponding carbobenzoxy-β-glutamine using thionyl chloride and triethylamine. By employing this method, β-carbobenzoxy-aminoglutarimide, N^1-benzyl β-carbobenzoxyaminoglutarimide, and N^1-propyl β-carbenzoxyaminoglutarimide were synthesized.

The synthesis of sulfanilyl-α-aminoglutarimide was effected by preparation of carbobenzoxy-α-amino glutarimide, hydrogenolysis of the carbobenzoxy group, reaction of the α-aminoglutarimide with p-nitro-benzenesulfonyl chloride, and catalytic hydrogenation of the nitro-group to give the desired sulfanilamide derivative.

PART I

CHAPTER I

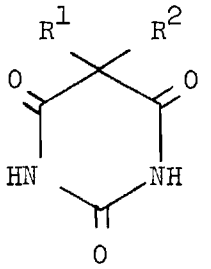
INTRODUCTION

Synergism is defined as the combined action of two or more agents that is greater than the sum of the action of the agents used alone. Synergistic effects are found in a wide variety of fields, including medicine. It is not uncommon to administer simultaneously two or more therapeutic agents to a patient to accomplish that which the agents could not do separately.

One example of such synergism involving the effects of barbiturates and sulfanilamides has been reported in several medical journals (1, 4, 5, 15). In brief, this synergism relates to the effect the sulfanilamides, which have no anesthetic properties of their own, have on reducing the dosage of Barbital needed to produce anesthesia or even death in test animals.

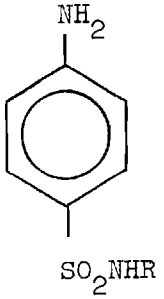
Concerning these two classes of compounds separately, certain substituted barbituric acids, more commonly known as barbiturates, possess physiological activity. The best known effect of barbiturates is their depressant action on the central nervous system which leads to their use as soporifics and sedatives (12). Barbiturates are also utilized for their bacteriostatic, antisclerotic, and antiinflammatory properties, and also for their use as in treatment for high blood pressure. Sulfanilamides (so called "sulfa" drugs) have been used during the last forty years as chemotheropeutic agents for the treatment

of diseases of protozoal and bacterial origin (17). Some common barbiturates and "sulfa" drugs are shown in Figures 1 and 2.



	R^1	R^2
Barbital	C_2H_5	C_2H_5
Phenobarbital	C_2H_5	C_6H_5
Amytal	C_2H_5	$(CH_3)_2CHCH_2CH_2$
Seconal	$CH_2=CH-CH_2$	$CH_3CH_2-CH-CH_3$

Figure 1. Common Barbiturates



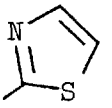
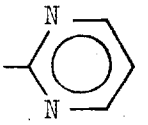
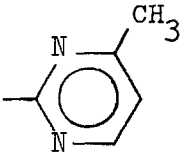
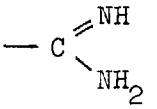
	R
Sulfathiazole	
Sulfadiazine	
Sulfamerizine	
Sulfaquanidine	

Figure 2. Common "Sulfa" Drugs.

The reported synergism of barbiturates and "sulfa" drugs has led to the work presented in this thesis, including the preparation of several new potentially therapeutic agents. These compounds are substituted 5-sulfanilamidobarbituric acids incorporating the barbiturate and the sulfa into a single molecule. To prepare these compounds it was necessary to work with 5-substituted and 5,7-disubstituted derivatives of 5-aminobarbituric acid, commonly known as uramil (Figure 3).

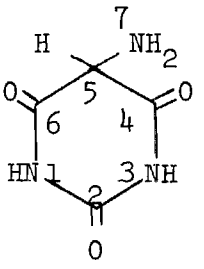
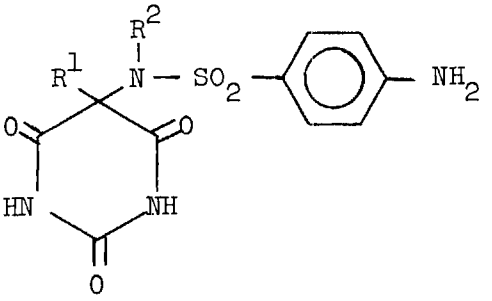


Figure 3. Uramil

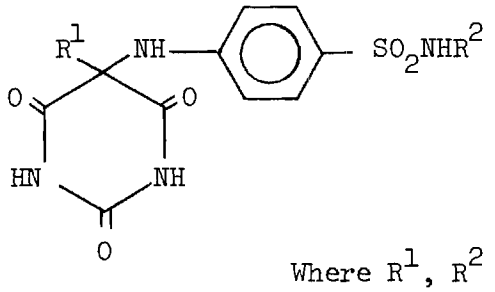
The ultimate goal of this work was the preparation of sulfanilyluramil derivatives of the type shown in Figure 4.



Where R^1, R^2 = H, alkyl, aryl

Figure 4. Sulfanilyluramils.

A second approach in incorporating a barbiturate and a sulfa into a single molecule is to prepare substituted 7-(4-benzenesulfonamido)-uramils (Figure 5). Unfortunately, the synthesis of these potentially interesting compounds was not successful and most of the work reported here was directed toward the synthesis of the previously described sulfanilyluramils.



Where R^1, R^2 = H, alkyl, aryl

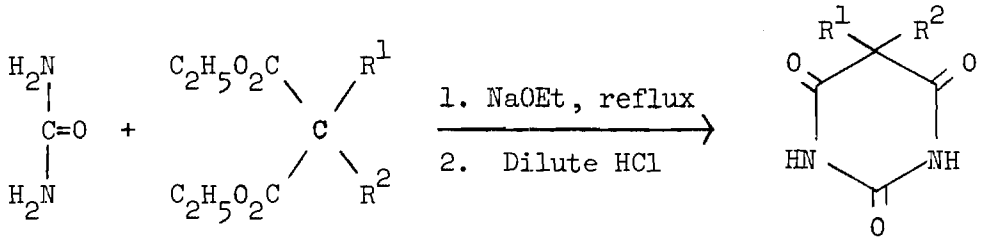
Figure 5. 7-(4-benzenesulfonamido)uramils.

The preparations of a variety of 7-substituted uramils have been reported in the literature. Uramil itself is usually prepared by the reaction of barbituric acid and aqueous sodium nitrite, followed by reduction with sodium thiosulfate (9). The synthesis of 5-alkyluramils is usually effected by the reaction of 5-alkyl-5-bromobarbituric acids with ammonia at a pressure of 2-3 atmospheres (20). The method of Gebauer, (14), in which 5-alkyl-5-bromobarbituric acids and primary or secondary amines are reacted in refluxing ethanol, offers a good pathway to 5,7-disubstituted uramils. Skinner and Lyman (20) have reported the synthesis of a series of 7-acyluramils by the condensation of 5-ethyluramil and an acyl

chloride in aqueous trimethylamine.

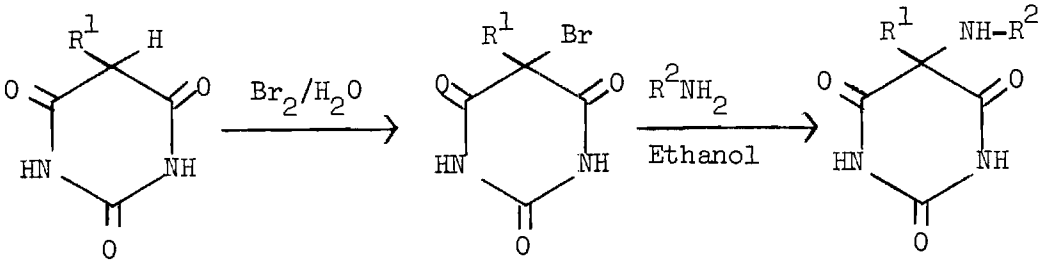
Of the most importance to this work was the synthesis by Doerr (11) of a series of 1,3,5-trialkyl-5-sulfanilamidobarbituric acids by condensation of the corresponding uramil derivative with N-acetylsulfanilyl chloride in pyridine, followed by subsequent hydrolysis of the acetamide group. Since most barbiturates which have useful physiological activity contain hydrogens on the imide nitrogens of the ring, it was desired to expand Doerr's work to attempt the synthesis of sulfanilamidobarbituric acids which were unsubstituted at the 3- and 5- positions. Prior to and during the time this program was in progress, no 5-alkylsulfanilyuramils or 5,7-dialkyl-sulfanilyluramils were reported in the literature.

In undertaking this problem, a knowledge of the methods for synthesis of barbituric acids, uramils, and sulfanilamides was necessary. This posed very little difficulty, since the literature contains many references to each type of synthesis. Figures 6, 7, and 8 give typical syntheses of each of these types of compounds.



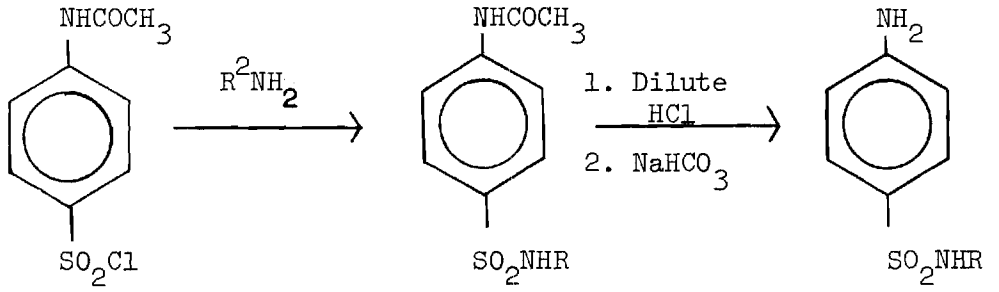
Where R^1, R^2 = H, alkyl, aryl

Figure 6. Synthesis of Typical Barbituric Acids.



Where R^1, R^2 = H, alkyl, aryl

Figure 7. Synthesis of Typical Uramils.



Where R = H, alkyl, aryl, etc.

Figure 8. Synthesis of Typical Sulfanilamides.

As previously indicated, no references were found for the synthesis of 7-(4-benzenesulfonamido)-uramils, and other than Doerr's work, no references were found for the synthesis of substituted sulfanilyluramils.

CHAPTER II

DISCUSSION OF EXPERIMENTAL INVESTIGATIONS

The first approach to the preparation of sulfanilyluramil derivatives was the attempted synthesis of sulfanilyluramil itself by condensation of urea and diethyl N-acetylsulfanilamido-malonate in dimethylsulfoxide. This proposed synthesis is shown in Figure 9.

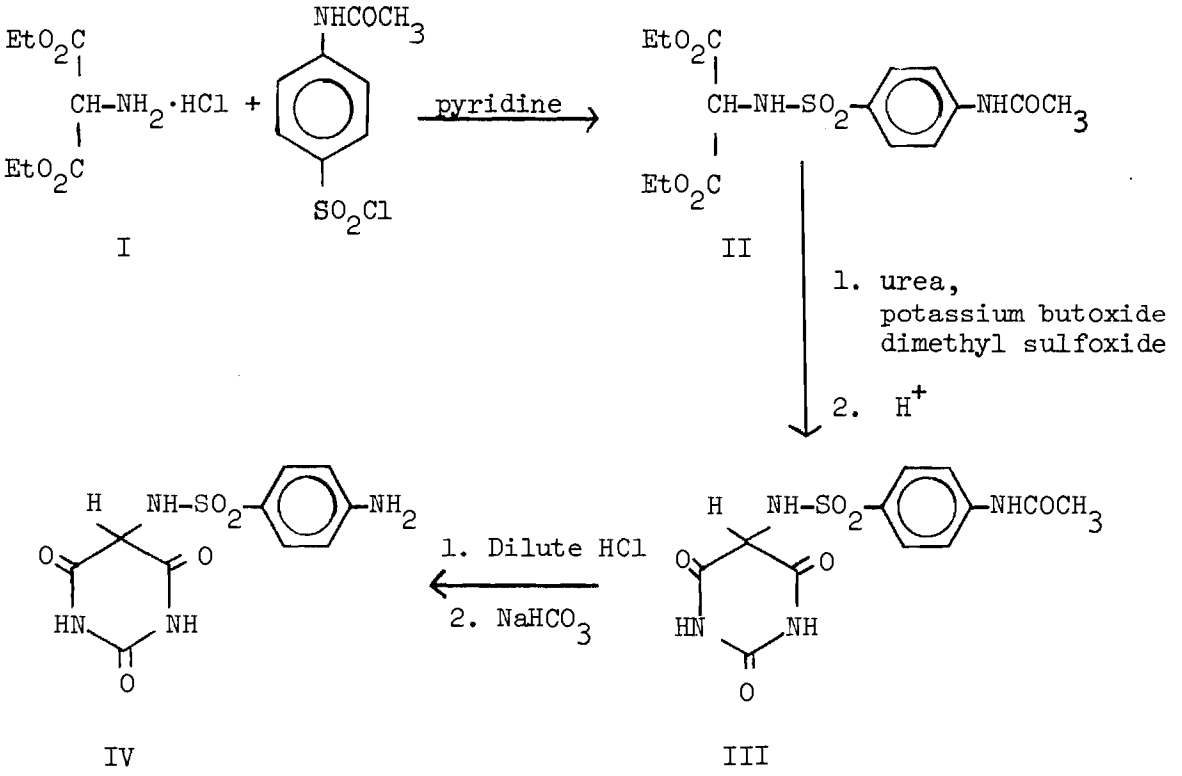


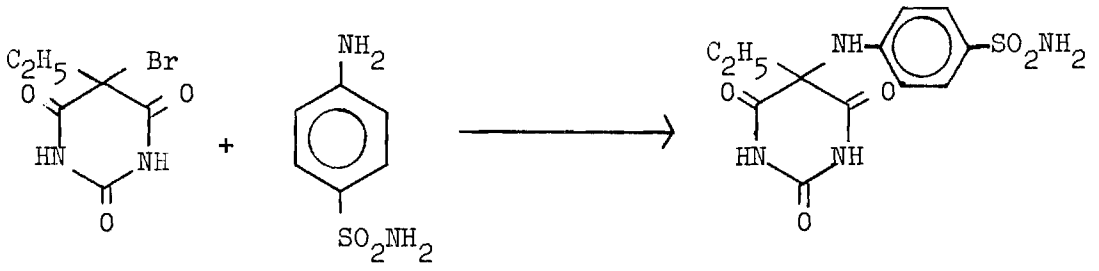
Figure 9. Proposed Path to Sulfanilyluramil.

Doerr (11) had attempted the condensation of diethyl N-acetylsulfanilamidomalonate and urea in refluxing sodium ethoxide solution, and had reported that under such reaction conditions the sulfonamide linkage was cleaved and the desired product was not formed. It was hoped that the milder reaction conditions developed by Beres, et al., (3), for the synthesis of barbituric acids at room temperature using potassium t-butoxide in dimethylsulfoxide, might give the desired condensation instead of cleavage of the sulfonamide. Unfortunately, the sulfonamide was also cleaved under these mild conditions, and none of the desired product could be isolated.

It is interesting to note that in some cases a product of this reaction was uramil. This product could have been formed either by the desired condensation followed by cleavage of the sulfonamide bond or by initial cleavage of the sulfonamide bond followed by condensation of the resulting diethyl aminomalonate and urea. Although no definite answer to this question was determined, it seems likely that had the desired condensation occurred first, at least some of the desired product could be isolated from the reaction mixture. Since this was not the case, the formation of uramil would appear to result from initial cleavage of the sulfonamide bond, followed by the condensation reaction to give the barbituric acid ring.

Concurrently with the above work, efforts were undertaken to prepare 5-ethyl-7-(4-benzenesulfonamido)-uramil. The proposed pathway to this compound is shown in Figure 10. This reaction pathway

was unsuccessful, for reasons which are not quite clear. Cox, et al. (8), have shown that the halogen atom in 5-ethyl-5-bromobarbituric acid is labile and undergoes displacement reactions in a normal manner. The reactivity of sulfanilamide in displacement reactions with 2,4-dinitrofluorobenzene has been shown by Brauniger and



V VI

Figure 10. Proposed Synethsis of 5-Ethyl-7-(4-benzenesulfonamido)-uramil.

Spangenberg (6). However, it should be noted that in this latter reference the aromatic ring of sulfanilamide is credited with aiding the reaction by stabilizing the transition state of the reaction. This type of stabilization would not be possible for the displacement of the halogen from a 5-alkyl-5-halobarbituric acid.

The lack of reaction between 5-bromo-5-ethylbarbituric acid and sulfanilamide is apparently not steric in nature, since Gebauer (14) has shown that the former reacts readily with a variety of alkyl-amines and aniline derivatives. The most likely reason for the failure of the desired reaction would appear to be the weak basicity

of the sulfanilamide molecule. This lack of basicity can be explained by resonance iteration such as that shown in Figure 11.

Figure 11. Resonance of Sulfanilamides

With the failure to produce sulfanilyluramil by condensation of urea and diethyl sulfanilamidomalonate, attention was directed toward the synthesis of 5-alkylsulfanilyluramils. Initial efforts were placed on the synthesis of sulfanilyluramils containing either a methyl or an ethyl group in the 5-position. An outline of this method starting from diethyl ethylmalonate is shown in Figure 12.

The preparation of 5-ethyluramil, X, or its methyl analog, was quite straightforward but attempts to condense either compound with N-acetylsulfanilyl chloride failed to give the desired product. One difficulty associated with this condensation reaction was the lack of an inert mutual solvent for the uramil derivative and the sulfonyl chloride. Solvents used in attempted condensations included pyridine, aqueous trimethylamine, PMF, and dimethylsulfoxide.

When this first approach to 5-alkylsulfanilyluramils proved to be unsuccessful, the reaction was attempted in acetic acid, a solvent

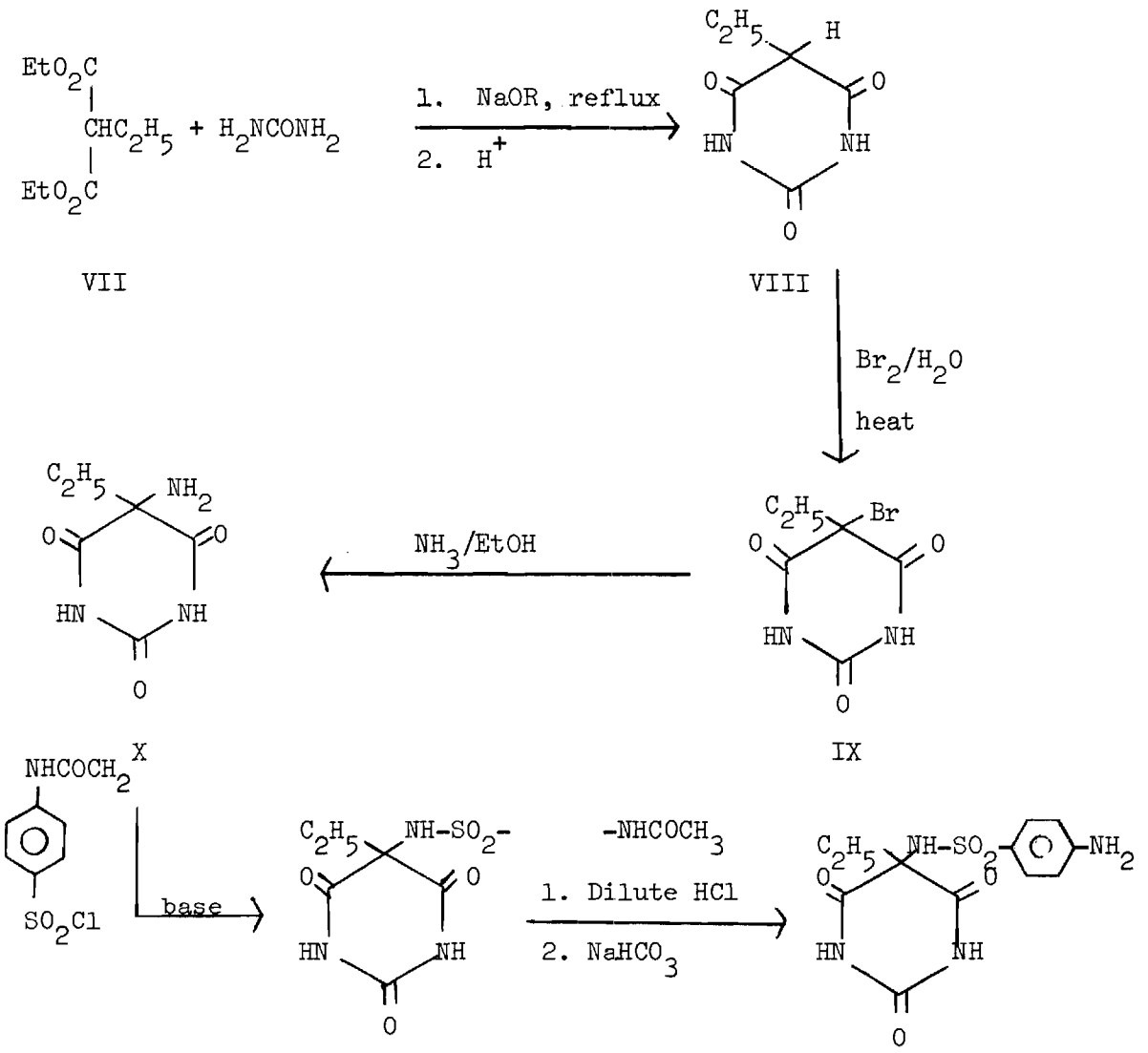


Figure 12. First Proposed Path to 5-Ethyl-7-sulfanilyluramil.

previously reported (18) as useful in the formation of sulfonamide derivatives of weakly basic amines. This synthetic scheme is shown in Figure 13. Unfortunately, the reaction failed to give the desired sulfonamide, XIV, instead the product isolated from the reaction mixture was the mixed anhydride of sulfanilic acid and acetic acid.

The failure of N-acetylsulfanilyl chloride to react with 5-methyluramil would appear to be due mainly to a lack of nucleophilicity and/or basicity of the 5-methyluramil. The problem cannot be one of steric hindrance since Doerr (11) has shown that 1,3,5-trimethyluramil forms a sulfonamide derivative quite readily under similar reaction conditions. However, the blame for the observed lack of reaction cannot lie wholly with the 5-methyluramil, since 5-ethyluramil is reported by Skinner (20) to react with chloroacetyl chloride in 35 percent yield to form the corresponding chloroacetamide. The probable reason for the failure of 5-methyluramil and N-acetylsulfanilyl chloride to undergo condensation under the previously described conditions is a combination of two factors: the lack of basicity of 5-methyluramil, and the lack of reactivity of the N-acetylsulfanilyl chloride.

The mild reactivity of the sulfonyl chloride is not unexpected. Most sulfonyl chlorides are less reactive than their acid chloride analogs. In the case of aromatic sulfonyl chlorides which contain an electron donating group on the benzenoid ring, resonance structures such as those shown in Figure 14 contribute to a decrease in the positive character of the sulfur atom, leading to a corresponding

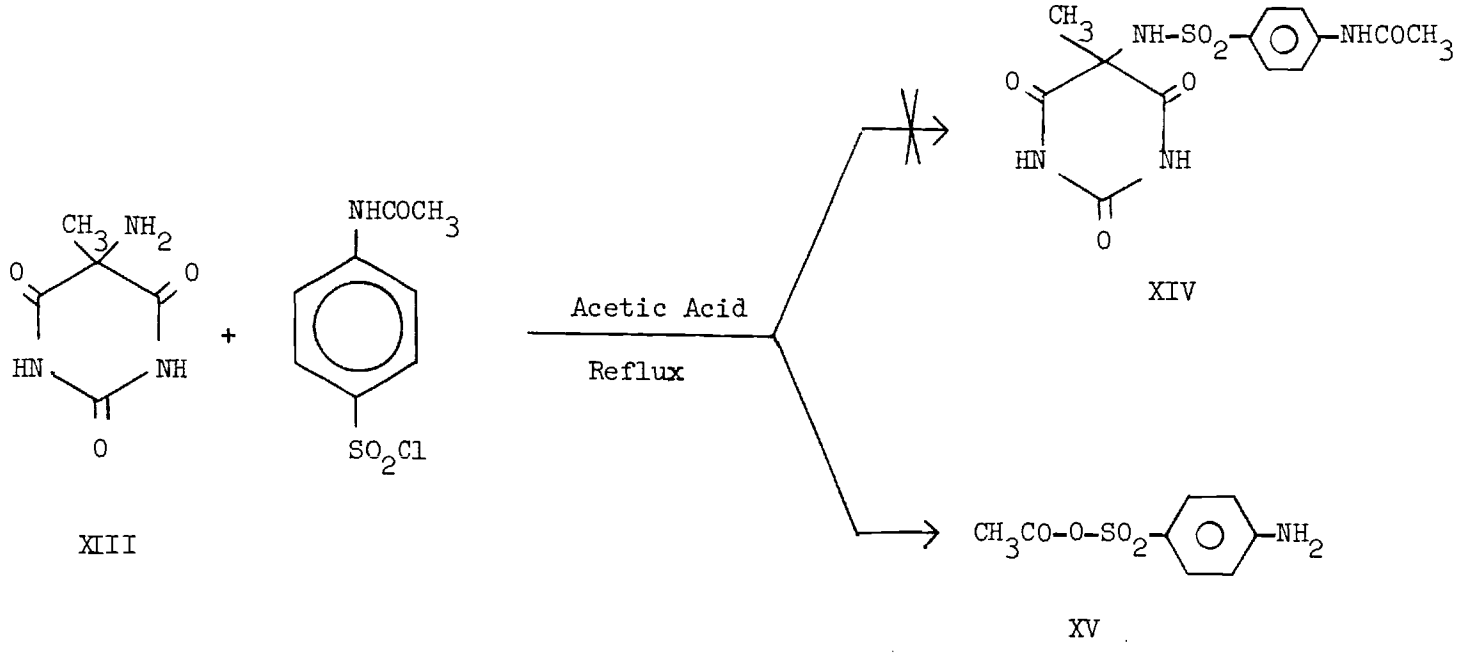


Figure 13. Reaction of 5-Methyluramil and N-acetyl-sulfanilyl Chloride in Acetic Acid.

decrease in the susceptibility of the sulfonyl chloride to attack by nucleophiles.

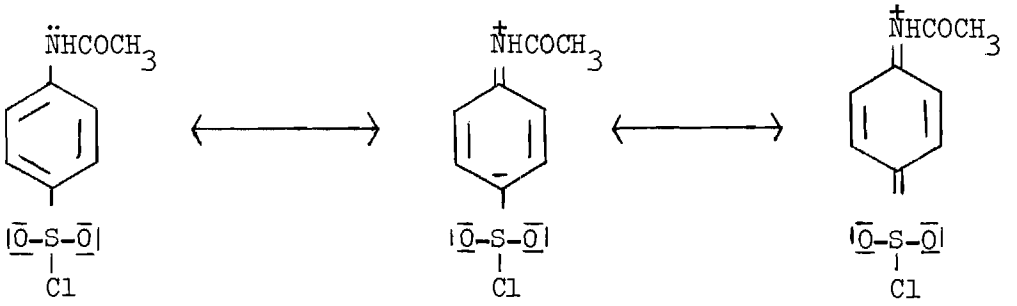


Figure 14. Resonance of Sulfanilyl Chlorides.

The lack of basicity and/or nucleophilicity of 5-alkyluramils is not readily explained. As previously mentioned, steric factors are apparently relatively unimportant since 1,3,5-trialkyluramils react quite well with N-acetylsulfanilyl chloride. As will be discussed in a later section, 5,7-dialkyluramils also undergo a smooth reaction with sulfonyl chlorides to give sulfonamide derivatives. These facts would appear to indicate that the lack of basicity of uramil derivatives is due mostly to electronic effects.

Cox, et al., (8) have reported evidence that the adjacent carbonyl groups exert a strong electron withdrawing influence on the 5-position of 5-alkyl-5-halobarbituric acids. This same electron withdrawing influence would be expected in 5-alkyluramils. The effect of an electron deficiency at C-5 would be to decrease the availability of the electron pair on the amine nitrogen, thus lowering the basicity

of the uramil derivative. This effect cannot completely explain the lack of reactivity of 5-alkyluramils, however, since diethyl aminomalonate reacts readily with N-acetylsulfanilyl chloride under similar reaction conditions.

Although 5-methyluramil is reported (19) to form a hydrochloride salt, solutions of 5-methyluramil are acidic in nature. The pH of an aqueous 0.1 M solution of 5-methyluramil was found to be 3.51, corresponding to a hydrogen ion concentration of 3.10×10^{-4} moles/liter. This datum indicates that the compound is appreciably ionized in solution and could conceivably exist in the form of a zwitterion, as shown in Figure 15.

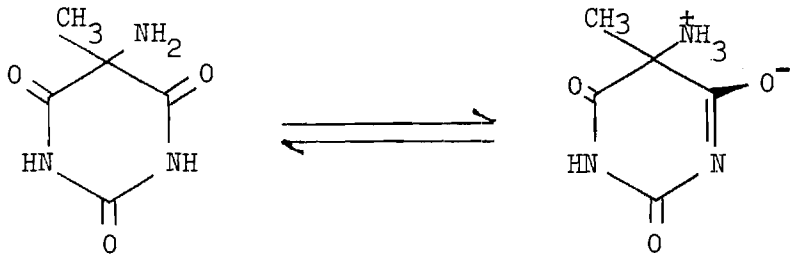


Figure 15. Formation of Zwitterionic 5-Methyluramil.

The IR spectra of 5-ethyluramil and 5-methyluramil do not have sharp absorptions in the N-H and C-O stretching regions. Doerr (11) has indicated that this lack of sharpness in these regions may be due to enolization of the alkyluramil molecule. Some of the possible structures resulting from enolization of 5-methyluramil are shown in Figure 16.

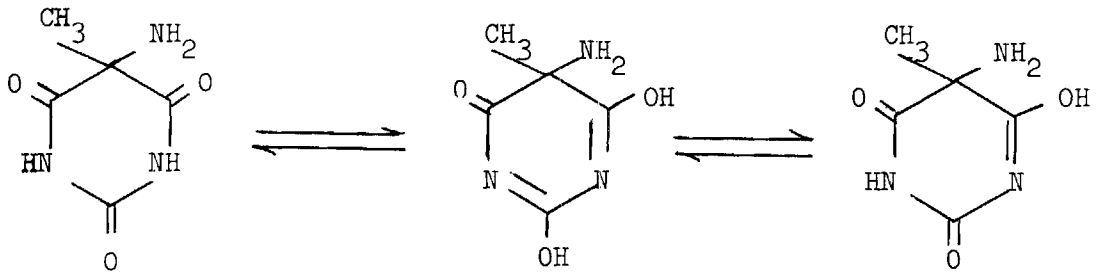
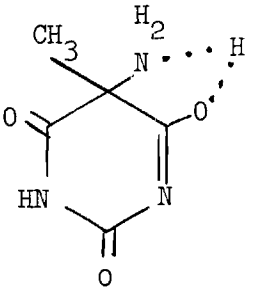


Figure 16. Enolized Forms of 5-Methyluramil.

One possible consequence of such an enolization could be a structure such as XVI, shown in Figure 17.



XVI

Figure 17. Possible Alternative 5-Methyluramil Structure.

Such a structure is purely speculative and only a much more thorough study would give a definite answer to the questions concerning the structure of uramils. A structure such as XVI could help explain the lack of basicity of 5-methyluramil since the electron pair on the amine nitrogen would be somewhat tied up by the enolic hydrogen.

At the present time this question remains unresolved.

When all efforts to condense 5-alkyluramils and N-acetylsulfanilyl chloride had proven unsuccessful, attention was shifted to 5,7-dialkyluramils. Somewhat surprisingly, these compounds were found to react fairly smoothly with N-acetylsulfanilyl chloride or with p-nitrobenzenesulfonyl chloride in pyridine at room temperature to give the desired sulfonamide derivatives. The starting disubstituted uramils were prepared by reacting a 5-alkyl-5-bromobarbituric acid with an alkyl amine in refluxing methanol for one to two hours.

Starting with 5-phenylbarbituric acid and 5-ethylbarbituric acid, 7-(N-acetylsulfanilyl)-5-phenyl-7-propyluramil and 7-(N-acetylsulfanilyl)-7-benzyl-5-ethyluramil were prepared by the method shown in Figure 18. The N-acetyl linkage was then selectively hydrolyzed in dilute hydrochloric acid to give the desired sulfanilamide, as shown in Figure 19.

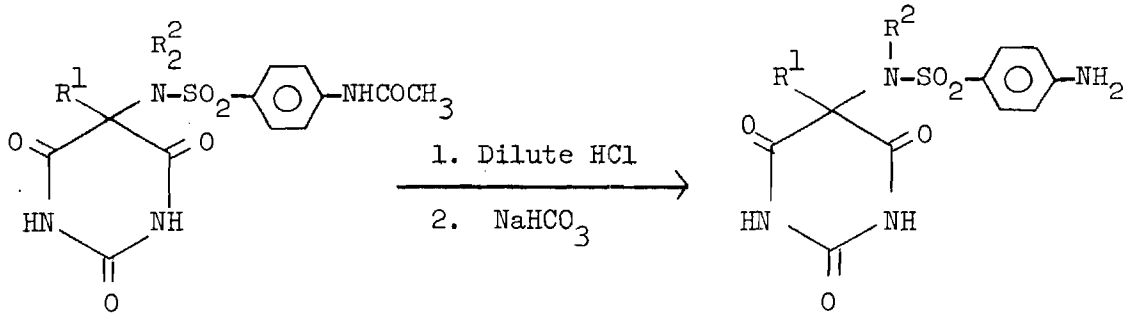
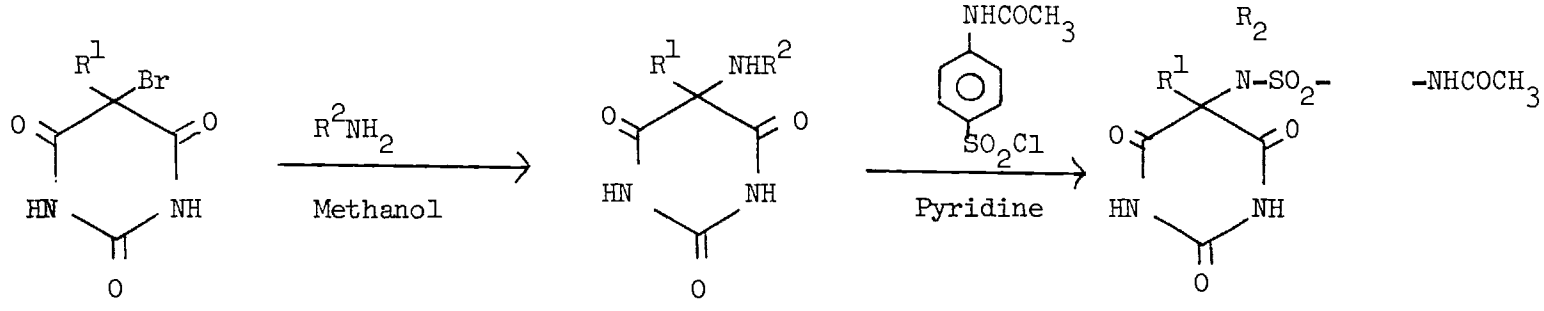


Figure 19. Hydrolysis of N-Acetylsulfanilyluramils.

It is interesting that the 5,7-disubstituted uramil derivative



R^1 = Phenyl, ethyl

R^2 = Propyl, benzyl

Figure 18. Synthesis of 5,7-Dialkyl-7-(N-acetylsulfanilyl)uramils.

react smoothly with sulfonyl chlorides while the somewhat simpler 5-substituted uramils apparently do not react under similar conditions. Several explanations are possible for this observation. One possibility is that the alkyl substituent on the amine nitrogen exerts an electron releasing effect which increases the basicity of the amine by increasing the availability of the electron pair. Such effects are well known for substituted organic amines. A second possibility may be due to the fact that the large alkyl group of the amine can, due to steric factors, reduce or eliminate the contribution of forms such as XVI to the structure of the uramil derivatives. This latter explanation, of course, assumes that structures such as XVI actually account for the lack of reactivity of 5-alkyluramils, and this assumption has not been proven.

In Table 1 are summarized all of the compounds, previously unreported, which were obtained during this investigation. Spectra of most of them are contained in the Appendix as indicated.

Table 1. New Compounds.

Compound	M.P.
Acetic Sulfanilyl Anhydride	239 - 240°
7-p-Nitrobenzenesulfonyl-5-phenyl-7-propyluramil	240 - 241°
7-N-Acetylsulfanilyl-5-phenyl-7-propyluramil	265 - 265.5°
5-Phenyl-7-propyl-7-sulfanilyluramil	205 - 206°

CHAPTER III

EXPERIMENTAL

All melting points are recorded in degrees Centigrade and are uncorrected. Melting points were determined in capillary tubes of 1.5-2.0 mm (OD) on a Mel-Temp melting point apparatus. To insure consistency the same thermometer was used for all melting point determinations. Elemental microanalyses were performed by Atlanta Micro-Laboratories, Atlanta, Georgia, unless otherwise noted. Infrared spectra were recorded using a Perkin-Elmer Model 700 spectrophotometer. Infrared Spectra of solid samples were determined employing potassium bromide pellets, spectra of liquids were determined employing liquid films on sodium chloride plates. Nuclear magnetic resonance spectra were obtained with a Varian Associates Model A-60D spectrometer. Mass spectral data was obtained using a Varian Associates Model M-66 mass spectrometer.

Attempted Preparation of 5-(N-Acetylsulfanilamido)-Barbituric Acid Under Basic Conditions

Synthesis of Diethyl N-Acetylsulfanilamidomalonate

Diethyl Isonitrosomalonate. This compound was synthesized using the method of Zambito and Howe (23). Starting from 200 g. (1.25 mole) of diethyl malonate, typical yields of crude product were on the order of 75 percent. No attempt was made to purify the

ester by distillation, instead, the crude product was used for subsequent reactions.

Diethyl Aminomalonate. Synthesis of this compound was effected by reduction of diethyl isonitrosomalonate, using the method of Hartung et al. (16). General conditions involved the reduction of 38 g. (0.20 mole) of the oxime a palladium catalyst in 200 ml. of dry ether, the resulting crude diethyl aminomalonate was isolated as its hydrochloride salt.

Diethyl Aminomalonate Hydrochloride. The general procedure of Hartung, et al. (16) was used for the preparation of this compound, with one modification. Acetone was used as the recrystallization solvent, rather than the mixed system described in the literature. Overall yields, based on diethyl malonate, averaged 33 percent. The recrystallized product was found to melt at 165-166°, (lit. (16) m. p. 163-164°).

Diethyl N-Acetylsulfanilamidomalonate. The method of Doerr (11) was essentially followed for this reaction. To 60 ml. of pyridine was added 16 g. (0.07 mole) of diethyl aminomalonate hydrochloride. Stirring was commenced and the flask was immersed in an ice bath. To the cold solution was added 17 g. (0.07 mole) of N-acetylsulfanilyl chloride. Upon complete solution, the flask was removed from the ice bath and the contents were stirred at 35° for 24 hours. The solution was poured into 325 ml. of ice water with vigorous stirring, whereupon a solid formed. The solution was chilled for one hour, then the tan solid was filtered off. The product was

washed with a small amount of iced water, dried, and recrystallized from toluene to give 21.5 gm (81 percent yield) of diethyl N-acetylsulfanilamidomalonate, m. p. 161-162° (lit. (11) m. p. 163.5-164.5°). An IR spectrum was identical to a spectrum of diethyl N-acetylsulfanilamidomalonate previously prepared by Doerr.

Attempted Condensation of Diethyl N-Acetylsulfanilamidomalonate with Urea in Dimethylsulfoxide

The general procedure was adapted from that of Beres, et al. (3) for the preparation of bariburic acids in dimethylsulfoxide. In a 100 ml. Erlenmeyer flask protected by a calcium chloride drying tube was placed 7.44 g. (0.02 mole) of diethyl N-acetylsulfanilamidomalonate and 6.0 g. (0.10 mole) of urea. The solids were dissolved in 35 ml. of dry dimethylsulfoxide, and a solution of 6.66 g. (0.060 mole) of potassium t-butoxide in 50 ml. of dimethylsulfoxide was added. The solution was stirred at room temperature for three hours during which time a deep purple color developed. The solution was poured into 200 ml. of iced water and was immediately acidified with hydrochloric acid. Upon acidification the color of the solution changed to a light pink hue and a precipitate began to form. After thorough chilling, the solution was filtered to give 0.30 g. of pink solid, identified as uramil by comparison of an IR spectrum with that of a known sample.

After the uramil was removed by filtration, the filtrate was extracted with three 300 ml. portions of ether. The ether extracts were dried over anhydrous magnesium sulfate and the ether was removed

on a rotary evaporator, leaving a brown oil which contained some dimethylsulfoxide. The oil was crystallized from water to give 30 mg. of tan solid, m. p. 95-100°. An IR spectrum was void in the carbonyl stretching region between 1690-1800 cm^{-1}, indicating the solid was not the desired product. The original reaction solution was also extracted with two 200 ml. portions of chloroform to give 0.01 g. of the same material isolated by ether extraction. Attempts to remove the water and dimethylsulfoxide from the extracted solution by means of rotovap led to extensive decomposition and the solution was finally abandoned.

Subsequent reactions gave similar results. The same unidentified product was obtained when dimethylurea was used in place of urea for the reaction, or when three equivalents of base were used. Decreasing the reaction temperature to just above the freezing point of dimethylsulfoxide gave results similar to those obtained at room temperature. In several instances small amounts (3-5 percent) of diethyl sulfanilamidomalonate were isolated from the reaction mixture along with the previously mentioned product. Similar results were obtained using dimethyl formamide as solvent, and subsequent work was done using the latter solvent. At no time, using either dimethylsulfoxide or N,N-dimethyl formamide, was a product isolated which had carbonyl absorptions present in the IR that would correspond to the desired N-acetylsulfanilyluramil.

Attempted Condensation of Diethyl N-Acetylsulfanilamidomalonate with Urea in N,N-Dimethyl Formamide

In a flask protected by a calcium chloride drying tube was placed 75 ml. of dry N,N-dimethyl formamide, 4.5 ml. (3.6 g., .044 mole) of t-butyl alcohol, and 1.68 g. (.043 mole) of clean potassium metal. When the potassium had dissolved, the solution was added to a chilled solution of 6.0 g. (0.10 mole) of urea and 5.3 g. (0.014 mole) of diethyl N-acetylsulfanilamidomalonate dissolved in 50 ml. of dry N,N-dimethyl formamide. The solution was warmed to room temperature and was stirred for three hours, during which time the color of the solution changed from turbid brown to a clear red color. The solution was acidified with hydrochloric acid and was filtered after several minutes to give 1.6 g. of uramil (identified by comparison with a known sample) and a pale yellow filtrate. The solvent was removed from the filtrate by means of a rotary evaporator attached to a vacuum pump, leaving a semi-solid yellow residue. The residue was dissolved in 50 ml. of boiling acetic acid and 10 ml. of water was added. The solution was chilled overnight and was filtered to give 0.8 g. of yellow solid, m. p. 210-212°. An IR spectrum showed the material to be the same product previously formed when dimethyl-sulfoxide was used as the reaction solvent.

After the solid has been removed by filtration the filtrate was evaporated to dryness on a rotary evaporator and 80 ml. of water was added to the residue. No water insoluble material was present, even after thorough chilling, and the solution was finally discarded.

The yellow solid which had been isolated was recrystallized twice from acetic acid to give 0.6 g. of pale yellow solid, m. p. 224-225°. An analysis[1] indicated the following composition.

Found: C,52.60; H,4.59:
N,7.62; S,17.32.

IR and NMR spectra showed that the amide portion of the starting malonate ester was still present in the product along with the aromatic ring. The largest m/e peak in the mass spectrum was observed at 300 amu. The product of these reactions was never conclusively identified, but appears to have resulted from a degradation of the diethyl N-acetylsulfanilamidomalonate.

This series of reactions were finally terminated when it became apparent that the desired product was not formed under the reaction conditions.

Attempted Synthesis of 5-Ethyl-7-(4-benzesulfonamido)-uramil Reaction of 5-Bromo-5-ethylbarbituric Acid and Sulfanilamide in Ethanol

In a 250 ml. round-bottomed flask fitted with a reflux condenser and a magnetic stirrer, were placed 200 ml. of absolute ethanol and 6.9 g. (0.04 mole) of sulfanilamide. The solution was heated to reflux and 4.70 g. (0.20 mole) of 5-bromo-5-ethylbarbituric acid was added. The solution was refluxed for 30 minutes, then was

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[1] Performed by Galbraith Laboratories, Knoxville, Tennessee.

cooled and stirred at room temperature overnight. The solution was filtered to give 1.70 g. of recovered sulfanilamide. The filtrate was evaporated to dryness on a rotary evaporator. The resulting residue was broken up and treated with 100 ml of dilute hydrochloric acid to dissolve any sulfanilamide which might be present. The solution was filtered and the resultant solid was dissolved in 30 ml. of 10 percent sodium hydroxide. The basic solution was filtered and the resultant solution was acidified, resulting in precipitation of 2.4 g. of 5-bromo-5-ethylbarbituric acid. No product containing both sulfonamide and carbonyl absorptions in it IR spectrum was isolated from the reaction, and the lack of formation of the hydrobromide salt of the sulfanilamide makes it unlikely that a reaction took place.

Reaction of 5-Bromo-5-ethylbarbituric Acid and Sulfanilamide in Aqueous Acetone.

The general procedure of Brauniger and Spangenberg (6) was followed for this reaction. To a solution consisting of 60 ml. of water and 120 ml. of acetone was added 4.16 g. (0.024 mole) of sulfanilamide, 5.64 g. (0.024 mole) of 5-bromo-5-ethylbarbituric acid, and 2.04 g. (0.025 mole) of sodium bicarbonate. The solution was heated to boiling and was refluxed for four hours. No visible change occurred during the period of refluxing. The solution was thoroughly chilled and was filtered to give 0.1 g. of white solid, m. p. 300°. An IR spectrum of the material was void in the usual range of sulfonamide absorptions. No further attempts were made to

identify this material. The remaining reaction solution was evaporated to dryness on a rotary evaporator, leaving a yellow residue. The solid was dissolved in 50 ml. of boiling water and was quickly filtered. After being thoroughly chilled, the solution was filtered to give 3.3 g. of sulfanilamide, identified by m. p. and comparison of an IR spectrum with that of a known sample. The filtrate was acidified with acetic acid and was again thoroughly chilled, but no precipitate appeared, and the reaction was terminated.

Attempted Preparation of 5-Methyl-5-(N-acetylsulfanilamido)-barbituric Acid by Direct Condensation

Synthesis of 5-Methyluramil

Diethyl methylmalonate. The method of Weiner (22) was used with several modifications. Methyliodide, instead of methylbromide, was used was the alkylating agent, and the product was washed with a 3 percent solution of sodium bisulfite before treatment with sodium hydroxide in order to destroy the iodine which was present. The reaction was performed using 4.4 moles of ethyl malonate, sodium, and methyl iodide. The diethyl methylmalonate was purified by vacuum distillation, b. p. 91.5°/16 mm. (lit. (22) b. p. 96°/16 mm.). Yields of several preparations ranged from 75 to 80 percent.

5-Methylbarbituric Acid. The general procedure of Dickey and Gray (10) was used with modifications. In a three-necked, five liter round-bottomed flask fitted with a dropping funnel, a mechanical stirrer, a condenser to which was attached a calcium chloride drying tube, and a heating mantle, 24.1 g. (1.05 mole) of freshly cut sodium

metal was reacted with three liters of anhydrous ethanol. To the ethoxide solution was slowly added 184 g. (1.05 mole) of diethyl methylmalonate over a period of 20 minutes. The solution was heated nearly to refluxing temperature and 65 g. (1.07 mole) of crystalline urea was added. A solid appeared after several minutes. The solution was refluxed, with stirring, for 12 hours. Afterwards, 500 ml. of water and 95 ml. of concentrated hydrochloric acid were added to dissolve the solids present. Most of the ethanol was distilled from the solution and the hot solution was filtered and then chilled thoroughly. The 5-methylbarbituric acid was collected and recrystallized from water containing a small amount of hydrochloric acid to give 75 g. (53 percent yield) of white needles, m. p. 200-202° (lit (10) m. p. 202-203°).

5-Bromo-5-methylbarbituric Acid. This procedure was based on the method of Cox, et al. (8) who reported the synthesis of various 5-bromobarbituric acids. In 1400 ml. of boiling water was dissolved 152 g. (1.07 mole) of 5-methylbarbituric acid. With continued heating and stirring, bromine was added slowly. After the addition of 50.0 ml. (0.94 mole) of bromine, the reddish bromine color persisted in the solution. Enough sodium bisulfite was added to remove all excess bromine. The solution was thoroughly chilled and filtered and the solid was dried, giving 147 g. (62.4 percent yield) of white 5-bromo-5-methylbarbituric acid, m. p. 186.5-188.0° (lit. (8) m. p. 190°).

5-Methyluramil. The method of Skinner and Lyman (20) was used for the synthesis of this compound. In a 400 ml. pressure bottle was placed 22.1 g. (0.10 mole) of 5-bromo-5-methylbarbituric acid and 300 ml. of absolute ethanol. The solution was cooled to -10°, and amonia gas was bubbled through the solution for 20 minutes. The bottle was immediately stoppered and clamped shut then was heated at 60° in a water bath. After five days the bottle was opened and the ethanol solution was filtered. The solid obtained by filtration was recrystallized twice from a minimum amount of boiling acetic acid to give 9.0 gm. (52 percent yield) of light pink powder, mp. 229-230° (lit. (11) m. p. 231°).

Attempted Reaction of 5-Methyluramil with N-Acetylsulfanilyl Chloride in Pyridine

The general procedure followed was that of Doerr (11). Typical experiments were performed as follows. In a round-bottomed flask protected by a calcium chloride drying tube were placed 10 ml. of dry pyridine and 1.0 g. (6.4 mmole) of 5-methyluramil. To the magnetically stirred solution was added 2.0 g. (8.5 mmole) of N-acetylsulfanilyl chloride which caused the solution to turn a deep purple color. The solution was stirred at 35° for seven hours, then was poured into 75 ml. of iced water. When no precipitate had formed after the solution was kept at 0° overnight, the solution was acidified with hydrochloric acid. No product precipitated from the acidified solution even upon prolonged cooling. Concentration of the aqueous solution occasionally led to recovery of a small amount of

the 5-methyluramil, but no reaction products whose IR spectra contained sulfamamide S-O stretching absorptions were ever isolated. The reaction was repeated several times with the same general results. Reaction time was varied from three hours to 24 hours and reaction temperatures were varied from room temperature to 65° with no success in isolating an identifiable product.

Attempted Condensation of 5-Methyluramil and N-Acetylsulfanilyl Chloride in Aqueous Trimethylamine

An attempt was made to react 5-methyluramil and N-acetylsulfanilyl chloride in aqueous trimethylamine since Skinner and Lyman (20) had reported the reaction of 5-ethyluramil and chloroacetyl chloride under similar conditions. In a typical reaction, 15 ml. of aqueous 2N trimethylamine was cooled in an ice bath to 0° and 3.14 g. (0.020 mole) of 5-methyluramil was added. The solution was stirred with a magnetic stirrer and 5.13 g. (0.022 mole) of N-acetylsulfanilyl chloride was added in portions over a 20 minute period. The solution was stirred at 0° for a total of 1.5 hours during which time it remained basic. The solution was then warmed to room temperature and stirred an additional 1.5 hours. At this point the solution was mildly acidic. The solution was filtered to give 1.5 g. of unreacted 5-methyluramil. The filtrate, after thorough chilling deposited more solid and was then filtered to give 1.1 g. of white solid, identified as sulfanilic acid by comparison with an authentic sample. Concentration of the filtered solution gave a small amount of additional 5-methyluramil, but no condensation products were isolated as indicated by the lack

of sulfonamide S=O stretching absorptions in the IR spectra. Varying the reaction time or increasing the reaction temperatures from 0° to room temperature gave similar results. Hydrolysis of the sulfonyl chloride was quite rapid at room temperature and was accompanied by a marked evolution of heat. No condensation products were ever obtained from this series of reactions.

Attempted Condensation of 5-Methyluramil and N-Acetylsulfanilyl Chloride in Acetic Acid

Acetic acid was investigated as a possible solvent for the reaction of N-acetylsulfanilyl chloride and 5-methyluramil. Shepherd (18) had earlier reported the use of acetic acid as a solvent in the preparation of sulfonamide derivatives of weak amines, using sodium acetate to neutralize the hydrogen chloride formed during the reaction. In a 50 ml. round-bottomed flask fitted with a heating mantle and reflux condenser, was placed 20 ml. of acetic acid and 2.0 g. (0.013 mole) of 5-methyluramil, and while stirred magnetically was heated to 100° to dissolve the uramil. Following addition of 3.7 g. (0.016 mole) of N-acetylsulfanilyl chloride, the solution was heated to reflux. The evolution of HCl was observed during the entire period the solution was refluxed. After 20 minutes, one-half equivalent of sodium acetate was added to the solution which now contained a precipitate, but the solution remained apparently unchanged. At ten minute intervals, 1/4, 1/8, 1/8, and 1/4 equivalents of sodium acetate were added to the refluxing solid. The last sodium acetate addition caused the solution to become clear, but almost immediately

a white precipitate formed. The solution was stirred and heated for 10 minutes after the last addition of sodium acetate, then two milliliters of water were added, giving a clear, dark colored solution. The solution was cooled thoroughly overnight. When no precipitate formed upon cooling, the solution was poured into 200 ml. of iced water. No product formed in the solution, even after extended cooling. Concentration of the solution on a rotary evaporator gave a trace of the starting 5-methyluramil as the only isolated material from the reaction.

The reaction was found to give an unexpected product if the sodium acetate addition was omitted. Investigation showed that the N-acetylsulfanilyl chloride and acetic acid reacted to give a mixed anhydride in which the amide of the sulfonyl chloride had been hydrolyzed. One preparation of this anhydride involved refluxing for 12 hours 60 ml. of acetic acid in which 3.75 g. (0.016 mole) of N-acetylsulfanilyl chloride had been dissolved. Soon after refluxing commenced a precipitate appeared in the solution. The amount of precipitate continued to increase during the reaction. The solution was filtered to give 3.2 g. of white solid. The product was purified by repeated washing with hot acetic acid. The purified product weighed 3.1 g (75 percent yield), m. p. 239-240°. The product was soluble in water in which it was slowly hydrolyzed to sulfanilic acid and acetic acid. The compound was hydrolyzed rapidly by aqueous base.

Important mass spectral peaks were observed at 21, 135, 93,

and 60 a.m.u. An NMR spectrum taken in pyridine-d_5 showed a four proton quartet at 2.6τ, a two proton singlet at 3.4τ, and a three proton singlet at 8.6τ. From this data the compound was determined to be acetic sulfanilic anhydride.

Calculated for $C_8H_9NO_4S$: C, 44.65; H, 4.19:
N, 6.51; S, 14.88:

Found: C, 44.50: H, 4.21:
N, 6.50; S, 14.76;

Attempted Reaction of Molten 5-Methyluramil and N-Acetylsulfanilyl Chloride

In a 25 ml. test tube was placed an intimate mixture of 2.0 g. (0.013 mole) of 5-methyluramil and 3.65 g. (0.016 mole) of N-acetylsulfanilyl chloride. The tube was immersed in a oil bath held at 200°C for one hour, during which time HCl was observed escaping from the tube. The tube and its contents were cooled. The gum-like solid which resulted was removed from the tube by scraping with a spatula. Upon recrystallization of the residue from water or acetic acid, only 5-methyluramil and some degradation products from the sulfonyl chloride were observed. None of the desired condensation product was ever found in or isolated from the reaction mixture, as indicated by the lack of an IR spectrum which contained both carbonyl and sulfonamide absorptions.

Attempted Preparation of 5-Ethyl-5-(N-acetylsulfanilamido)-Barbituric Acid by Direct Condensation

Synthesis of 5-Ethyluramil

5-Ethylbarbituric Acid. The general procedure of Dickey and Gray (10) was followed again for this synthesis. Into a three-necked, five liter, round-bottomed flask fitted with a dropping funnel, a mechanical stirrer, a heating mantle, and a condenser to which was attached a calcium chloride drying tube, was distilled three liters of anhydrous ethanol. To the ethanol was added 11.5 g. (0.50 mole) of freshly cut sodium metal, followed, after all the sodium had dissolved, by 94.1 g. (0.50 mole) of diethyl ethylmalonate which was added to the solution over a period of 30 minutes. When the addition of the malonic ester was complete, 30.0 g. (0.50 mole) of solid urea was added to the solution. Heat was applied and the solution was stirred vigorously. About 10 minutes after heating had commenced a white precipitate formed in the previously homogeneous and colorless solution. The solution was refluxed, with stirring, for a period of five hours. The flask was then equipped for distillation and two liters of ethanol was removed from the flask. At this point 500 ml. of water and 45 ml. of concentrated hydrochloric acid were added to the flask, dissolving the solid which was present. Distillation was resumed until a total of three liters of solvent had been collected. The solution was thoroughly chilled and was then filtered to give 50.0 g. (64 percent yield) of unrecrystallized white solid, m. p. 179-181° (lit. (10) m. p. 182°). The 5-ethylbarbituric acid was brominated

without further purification.

5-Bromo-5-ethylbarbituric Acid. The method of Cox, et al. (8) was used for this reaction. In a magnetically stirred two liter flask was placed 170 g. (1.10 mole) of 5-ethylbarbituric acid and one liter of water. The solution was heated and stirred until the solid had dissolved, then bromine was added to the hot solution. After the addition of 45 ml. (0.80 mole) of bromine, the solution became reddish-brown in color. Bromine addition was halted and sodium bisulfite was added to destroy the excess bromine in the solution. The flask was placed in an ice bath and the contents were thoroughly chilled. The solution was filtered and the product was recrystallized from ethanol to give 216 g. (83 percent yield) of 5-bromo-5-ethylbarbituric acid, m. p. 204-205° (lit. (8) m. p. 202°).

5-Ethyluramil. In a 400 ml. pressure bottle was placed 23.5 g. (0.10 mole) of 5-bromo-5-ethylbarbituric acid and 75 ml. of absolute ethanol which had been saturated at 0° with ammonia. The bottle was quickly stoppered and clamped, then was vigorously shaken to dissolve the barbituric acid. The bottle was immersed, with occasional shaking, for three days in a water bath maintained at 60°. After standing two additional days at room temperature, the bottle was opened and the solid which had formed was removed by filtration. The crude product thus obtained was twice recrystallized from acetic acid to give 8.6 g. (50 percent yield) of 5-ethyluramil, m. p. 200-202° (lit. (20) m. p. 216°). This melting point could not be raised by further recrystallization from acetic acid; however, when a small

sample was recrystallized from water, a white, granular powder, m. p. 216-217°, was obtained. It appears likely that the material recrystallized from water may be a hydrated form of the product.

Attempted Reaction of 5-Ethyluramil and N-Acetylsulfanilyl Chloride in Pyridine

In general, attempts to react 5-ethyluramil with N-acetylsulfanilyl chloride met with the same lack of success found with 5-methyluramil under similar conditions. In a typical reaction, 1.7 g. (0.010 mole) of 5-ethyluramil was dissolved in 15 ml of dry pyridine. To the stirred solution was slowly added 2.6 g. (0.011 mole) of N-acetylsulfanilyl chloride. The solution was stirred four hours at room temperature, during which time the solution turned a dark red color. The reaction mixture was poured into 30 ml. of iced water and was quickly acidified with hydrochloric acid. When thorough chilling produced no precipitated product, the solution was concentrated to one-third its original volume on a rotary evaporator and was chilled again. Only a very small amount of 5-ethyluramil was recovered from the solution, and the reaction was finally abandoned. The reaction was repeated several times with identical results. Longer reaction times and/or reaction temperatures of 40° also failed to give any product containing the desired sulfonamide absorptions in its IR spectrum.

Attempted Condensation of 5-Ethyluramil and N-acetylsulfanilyl Chloride in Dimethylsulfoxide

To 10 ml. of dry dimethyl sulfoxide, contained in a flask protected by a drying tube, was dissolved 1.7 g. (0.01 mole) of

5-ethyluramil and 2 ml. (2.0 g. 0.026 mole) of pyridine. To this solution was added over a 20 minute period a solution of 3 g. (0.013 mole) of N-acetylsulfanilyl chloride in 20 ml. of dimethylsulfoxide. The solution was stirred at room temperature for three hours, then was poured into 150 ml. of iced water. The solution was quickly acidified with hydrochloric acid, then was thoroughly chilled. No precipitate formed in the solution even after prolonged cooling. Attempts to remove the solvent on a rotary evaporator with the aid of a vacuum pump caused the solution to turn black and emit a foul odor. No condensation product which contained both sulfonamide and carbonyl absorptions in its IR spectrum was ever recovered under these reaction conditions.

Synthesis of 5,7-Disubstituted-7-sulfanilyluramils

Synthesis of 5-Phenyl-7-propyl-7-sulfanilyluramil

5-Phenyl-7-propyluramil. The method of Walker (21) was employed for this synthesis. To a solution of 15 g. (0.054 mole) of 5-bromo-5-phenylbarbituric acid in 60 ml. of methanol contained in a 100 ml. round bottomed flask fitted with a reflux condenser, was added 8.80 ml. (6.3 g., 0.108 mole) of n-propyl amine. The magnetically stirred solution was heated to boiling and was refluxed one hour. The solution was cooled overnight then the methanol was removed on a rotary evaporator, leaving a white wolid. The product was thoroughly stirred and shaken with 200 ml. of water to remove unreacted amine and its hydrobromide salt. The water-insoluble solid was separated by filtration and was dissolved in 200 ml. of boiling ethanol. After the

addition of 200 ml. of hot water, the solution was filtered and was chilled overnight. Filtration of the cold solution gave 10.0 g. (70.0 percent yield) of white crystals, m. p. 182-183° (lit. (21) m. p. 183°).

The NMR spectrum, obtained in Dimethylsulfoxide-d_6, contained absorptions at 11.3δ(broad, 2H), 7.3δ(singlet, 5H), 2.6δ(broad, 1H), 2.3δ(multiplet, 2H), 1.3δ(multiplet, 2H), and 0.8δ(triplet, 3H).

7-p-Nitrobenzenesulfonyl-5-phenyl-7-propyluramil. The procedure utilized by Doerr (11) for the preparation of sulfanilamide derivatives of alkylated uramils was used for this reaction. In a 50 ml. round-bottomed flask fitted with a magnetic stirrer was placed 20 ml. of dry pyridine and 3.0 g. (0.011 mole) of 5-phenyl-7-propyluramil. When all the solid was dissolved, 3.3 g. (0.015 mole) of p-nitrobenzenesulfonyl chloride was added during a one minute period causing a slight increase in the temperature of the solution. The solution was stirred overnight at room temperature, then was added dropwise to an ice-cold solution of hydrochloric acid, causing immediate formation of a precipitate. The solution was thoroughly chilled and was filtered to give 3.2 g. of yellow solid. After several attempts to recrystallize the material from ethanol-water or methanol-water solutions had failed, the crude product was subjected to chromatography on silica gel, using ether, ethyl acetate, and ethanol to elute the material from the column. Three bands, (2.0, 0.5, and 0.3 g. of solid respectively) were eluted during the chromatography yielding 2.8 g. of solid. The latter two bands were discarded after IR spectra were found to be void in the sulfonamide S-O stretching region. The solid from the first

band eluted was dissolved in a minimum amount of hot methanol and enough water to produce a slight turbidity was added. The solution was made clear by the addition of a small additional amount of methanol, then was cooled in an ice bath. An oil settled out while the solution was still warm, and was separated by decanting the remaining solution into another flask. Further cooling of the decanted solution led to the recovery of 0.3 gm. of impure 5-phenyl-7-n-propyluramil. The oil which had separated was twice more recrystallized from aqueous methanol to give 0.10 g. (1.0 percent yield) of pale yellow crystals, m. p. 240-241°. Major IR absorptions were at 1720, 1540, 1415, 1350, 1175, and 855 cm^{-1}. Important peaks in the mass spectrum were observed at 402 and 308 amu.

The NMR spectrum obtained in dimethylsulfoxide-d_6 contained absorptions at 11.6 (singlet, 2H), 8.0 (multiplet, 4H), 7.2 (singlet, 5H), 2.8 (broad, 2H), 1.0 (broad, 2H) and 9.3 (triplet, 3H).

Calculated for $C_{19}H_{18}N_4O_7S$: C, 51.12; H, 4.04;
N, 12.56; S, 7.17.

Found: C, 51.27; H, 4.11;
N, 12.57; S, 7.33.

No attempt was made to convert the 7-p-nitrobenzenesulfonyl-5-phenyl-7-propyl uramil to the corresponding sulfanilamide, since a better synthetic pathway was discovered utilizing N-acetylsulfanilyl chloride in place of p-nitrobenzenesulfonyl chloride.

7-N-Acetylsulfanilyl-5-phenyl-7-propyluramil. To a 25 ml. round-bottomed flask equipped with a magnetic stirrer and a calcium chloride drying tube was added 4.45 gm. (.017 mole) of 5-phenyl-7-propyluramil and 15 ml. of dry pyridine. The solution was stirred until the solid had dissolved, then 4.5 g. (0.019 mole) of N-acetylsulfanilyl chloride was added in one portion. The solution was stirred overnight at room temperature and was then slowly poured into 100 ml. of cold, dilute hydrochloric acid. A precipitate formed immediately in the acidified solution. After being chilled for several hours, the solution was filtered to give 5.5 g. of white solid, m. p. 185-190°. The product was recrystallized twice from aqueous ethanol to give 4.85 g. (62 percent yield) of pale yellow crystals, m. p. 265-265.5°. Important IR absorptions were observed at 1725, 1600, and 1540, (C=O stretch), and 1335, and 1170 cm^{-1}(S=O stretch).

The NMR spectrum, obtained in dimethylsulfoxide-d_6, showed absorptions at 11.6 (singlet, 2H), 7.3 (singlet, 4H), 7.2 (singlet, 4H), 2.7 (broad, 2H), 1.2 (multiplet, 2H), 1.1 (singlet, 3H), and 0.8 (triplet, 3H).

Calculated for $C_{21}H_{22}N_4O_6S$: C, 55.02; H, 4.80;
N, 12.23; S, 6.99.

Found: C, 55.21; H, 4.97;
N, 12.12; S, 6.87.

The product was found to be quite hygroscopic.

5-Phenyl-7-propyl-7-sulfanilyluramil. The procedure of Cason and Rapoport (7) for the N-acetyl cleavage of sulfanilamides was used with slight modification. In a 250 ml. round-bottomed flask equipped with a heating mantle, a reflux condenser, and a magnetic stirrer was placed 2.88 g. (6.3 mmole) of 7-(N-acetylsulfanilyl)-5-phenyl-7-propyluramil. To the solid was added a solution of 14 ml. of concentrated hydrochloric acid dissolved in 180 ml. of water. Refluxing was commenced and was continued until all of the solid had dissolved. Complete hydrolysis of the amide required 2.5 hours under these conditions. The hot solution was filtered and then neutralized to pH 8.0 using powdered sodium bicarbonate, resulting in formation of a precipitate. The solution was chilled overnight and was filtered to give 2.33 g. of pale yellow solid, m. p. 204-206°. The product was recrystallized from a minimum amount aqueous ethanol to give 2.05 g. (78 percent yield) of white solid, m. p. 205-206°. IR absorptions of importance occurred at 1720, 1625, 1600 cm^{-1} (carbonyl C=O stretch), and 1320 and 1150 cm^{-1} (sulfonamide S=O stretch).

The NMR spectrum in dimethylsulfoxide-d_6 contained absorptions at 11.6 (singlet, 2H), 7.3 (singlet, 4H), 7.2 (singlet, 4H), 5.0 (broad, 2H), 2.6 (multiplet, 2H), 1.3 (multiplet, 2H), 2.6 (multiplet, 2H), 1.3 (multiplet, 2H), and 0.8 (triplet, 3H).

Calculated for $C_{19}H_{20}N_4O_5S$: C, 54.81; H, 4.81
N, 13.46; S, 7.69.

Found: C, 55.05; H, 4.97;
N, 13.33; S, 7.77.

Synthesis of 7-Benzyl-5-ethyl-7-sulfanilyluramil

7-Benzyl-5-ethyluramil. The method of Walker (21) was used for the preparation of this compound. In 50 ml. of methanol was dissolved 10.0 g. (0.042 mole) of 5-bromo-5-ethylbarbituric acid. To the stirred solution was added 9.0 g. (0.085 mole) of benzylamine, causing formation of a white precipitate after about five minutes. The solution was heated to reflux, causing the precipitate to dissolve. After refluxing for two hours, during which time another precipitate appeared, the solution was cooled and filtered. The solvent was removed on a flash evaporator leaving an orange solid. The solid was crystallized twice from dilute ethanol to give 2.1 g. (20 percent yield) of tan crystals, m. p. 213-214°, lit. (21) m. p. 214°. An infrared spectrum of the product was identical to the spectrum of a known sample.

7-Benzyl-5-ethyl-7-(N-acetylsulfanilyl)-uramil. In a flask protected by a calcium chloride drying tube were placed 15 ml. of dry pyridine and 1.95 g. (7.5 mmole) of 7-benzyl-5-ethyluramil. To the magnetically stirred solution was added 2.0 g. (8.6 mmole) of N-acetylsulfanilyl chloride. The solution was stirred overnight at room temperature, then was poured into an ice cold solution of dilute hydrochloric acid. A solid formed almost at once in the acidified solution. The solution was filtered to give 1.5 gm. of brown solid which gradually turned to a dark oil. The product was recrystallized twice from aqueous ethanol to give 0.71 g. of grey solid, m. p. 159-165°. An IR spectrum of the obviously impure product showed sulfonamide S=O stretching absorptions at 1160 and 1320 cm^{-1} and

carbonyl C=O stretching absorptions at 1700 cm^{-1}, indicating that the desired reaction probably did occur. The product was recrystallized from dilute ethanol to give 0.5 g. of yellow crystals, m. p. 163-166°. Further recrystallizations gave no additional sharpening of the melting point of the material. A mass spectrum of the product showed a peak at m/e 458. The material was submitted for analysis.

Calculated for $C_{21}H_{22}N_4O_6S$: C, 55.02; H, 4.80;
N, 12.23; S, 6.99.

Found: C, 53.90; H, 5.02;
N, 11.90; S, 6.87.

Although not enough sample remained for further purification, it seems quite probable that the crude product is the desired product.

CHAPTER IV

CONCLUSIONS

The two methods that originally seemed feasible for the preparation of 5-alkyl-5-(N-acetylsulfanilamido)barbituric acid derivatives, from which 5-alkyl-5-sulfanilamidobarbituric acids could be obtained by hydrolysis, have been unsuccessfully investigated: direct condensation of a 5-alkyluramil with N-acetylsulfanilyl chloride; and cyclization of diethyl N-acetylsulfanilamidomalonate with urea in dimethylsulfoxide in the presence of potassium t-butoxide.

Suitable procedures for the reaction of 5,7-dialkyluramils and N-acetylsulfanilyl chloride to give several 5,7-dialkyl-7-sulfanilyluramils have been developed.

Spectra have been recorded for the new barbituric acids: IR absorptions from an S=O stretch of sulfonamide at approximately 1350 cm^{-1} and 1150 cm^{-1} and from a C=O stretch of the barbituric acid ring at 1700 cm^{-1} were found to be most useful in elucidating structures. The carbonyl C=O absorptions in 5,7-dialkyluramils were much sharper than the carbonyl absorptions of 5-alkyluramils.

The structure of 5-alkyluramils does not appear to be that of a free amine, based on its lack of basicity and nucleophilicity.

CHAPTER V

RECOMMENDATIONS

It is felt that additional potential "sulfa" drugs could be produced by the procedures developed during this work. It is predicted that N-succinoylsulfanilyl chloride could be substituted in place of the N-acetylsulfanilyl used in this work. Such a substitution would give a potential "sulfa" drug which could readily form a water soluble derivative. Also, the use of N-succinoylsulfanilyl chloride would result in a shorter synthesis, since the final product would result from the condensation of the uramil derivative and the sulfanilyl chloride.

The determination of the actual structures of 5-alkyluramil derivatives and the corresponding 5,7-dialkyl derivatives would be of considerable interest also, especially in attempts to relate the obvious chemical differences in the two types of compounds.

It would be of interest to obtain data regarding the physiological activities of the new potential therapeutic agents which were prepared during the course of this investigation.

APPENDIX A

INFRARED SPECTRA

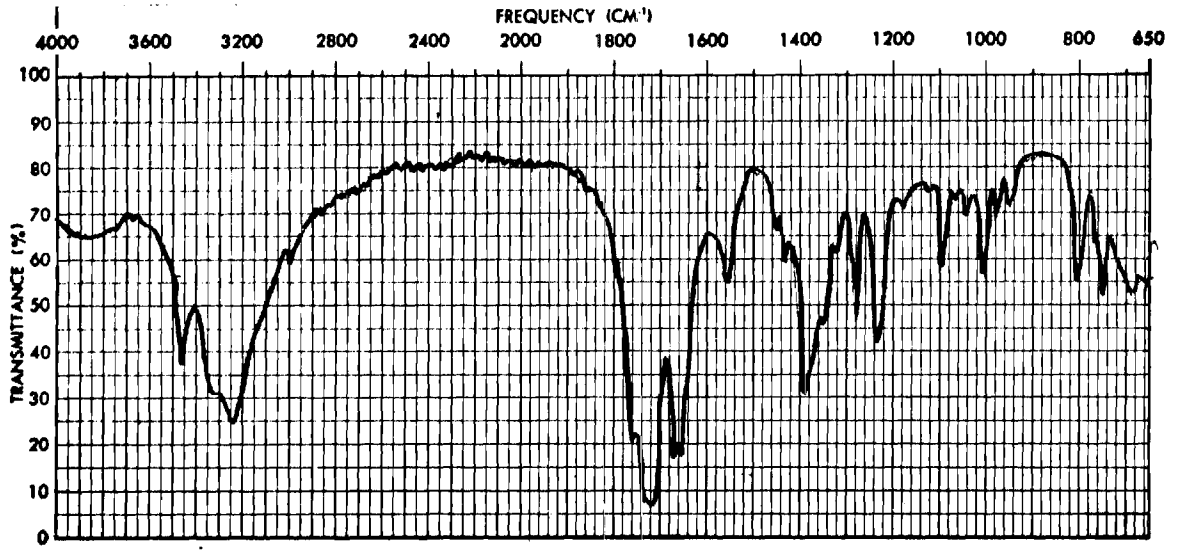

Figure 20. Infrared Spectrum of 5-Ethyluramil.

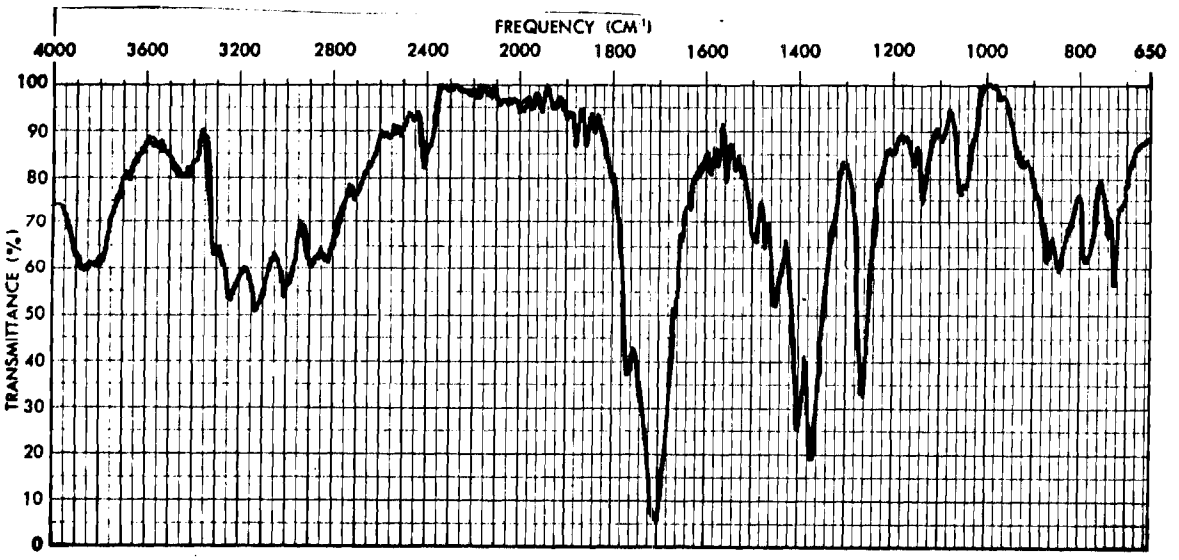

Figure 21. Infrared Spectrum of 5-Phenyl-7-propyluramil.

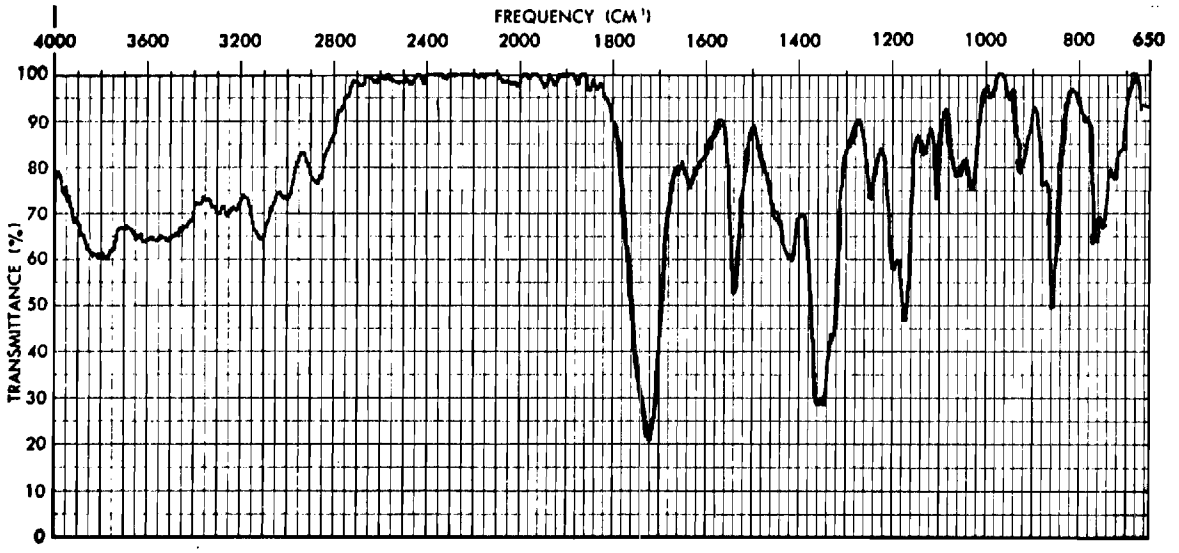

Figure 22. Infrared Spectrum of 7-(p-Nitrobenzene-sulfonyl)-5-phenyl-7-propyluramil.

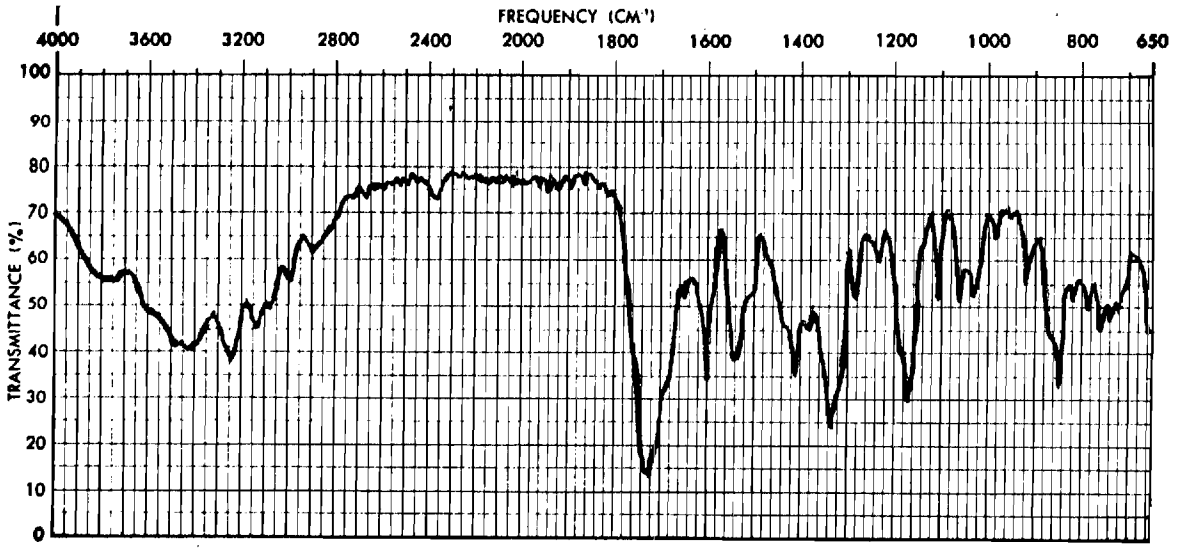

Figure 23. Infrared Spectrum of 7-(N-Acetylsulfanilyl)-5-phenyl-7-propyluramil.

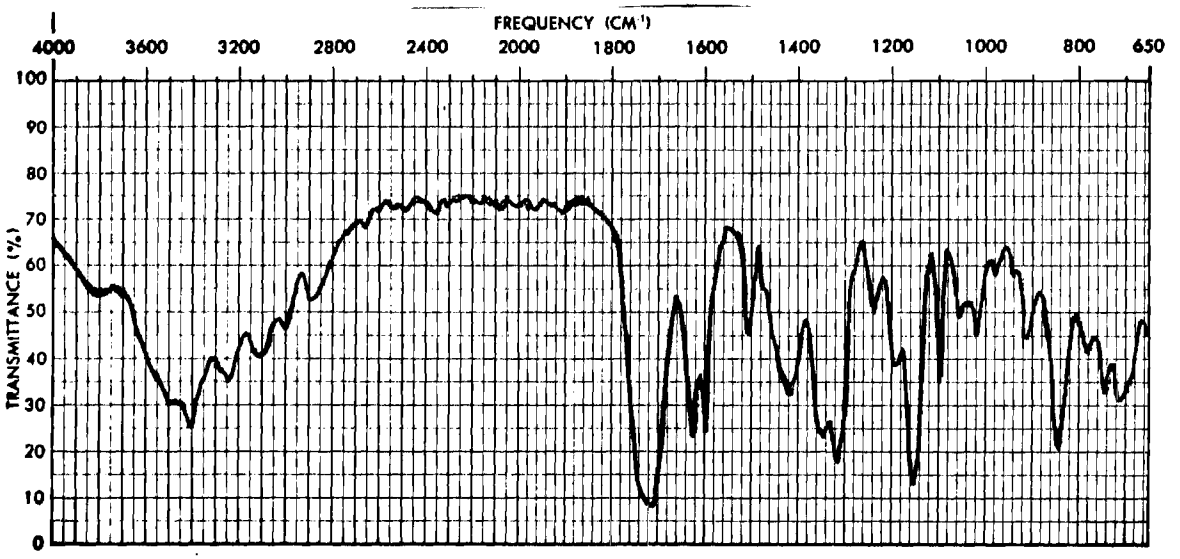

Figure 24. Infrared Spectrum of 5-Phenyl-7-propyl-7-sulfanilyluramil.

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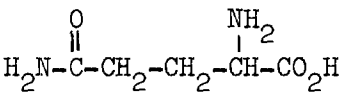
PART II

CHAPTER I

INTRODUCTION

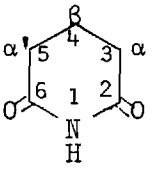
Glutamine (Figure 1) and glutarimide (Figure 2) are compounds first described in the literature, (6, 35) over 80 years ago.



I

Figure 1. Structure of Glutamine.

Since that time a large number of derivatives of each compound have been reported. In the last 15 years, new importance has been attached to these classes of compounds after it was discovered that certain



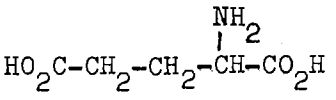
II

Figure 2. Structure of Glutarimide.

derivatives of glutamine and glutarimide possessed useful physiological activity. This activity will be discussed separately for each type of

compound.

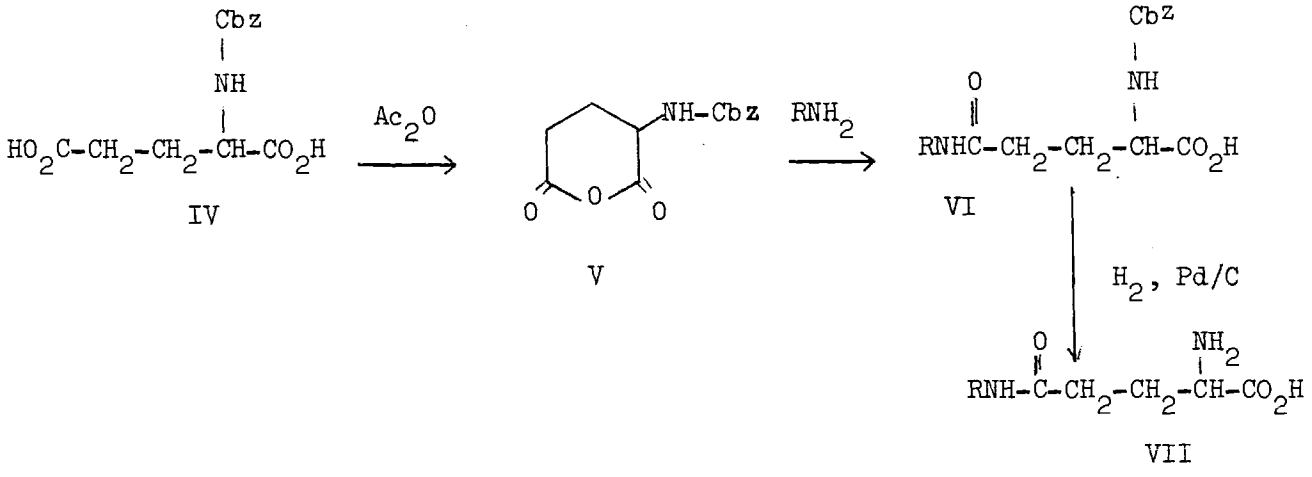
Glutamine occurs naturally as L-(+)-glutamine, a commonly occurring amino acid. Fruton (18) has reported the successful synthesis of L-(+)-glutamine. Although the literature contains many references to reactions of glutamine itself and to preparations of relatively simple derivatives, much of the present day literature appears concerned with glutamine as a component of peptide and polypeptide chains. Closely related to many of the reactions of glutamines are the reactions of glutaric acid derivatives and aminoglutaric acids, such as glutamic acid, III.



III

Figure 3. Structure of Glutamic Acid.

A considerable number of preparations of N-substituted glutamine derivatives has been reported in the literature, the procedure of Edelson et al. (14) being typical of these syntheses. Using this method, the substituted glutamine is prepared by reacting carbobenzoxy glutamic anhydride with an amine in a suitable solvent, followed by hydrogenolysis of the carbobenzoxy group. This synthesis is shown in Figure 4. Many similar syntheses involving glutamic acids and glutamines require the use of an easily removable group such as the carbobenzoxy for the protection and inactivation of the amine function-



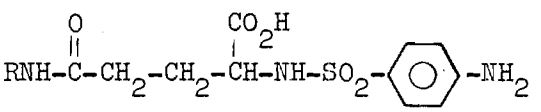
Where R = alkyl, aryl; C^{bz} = $-CO_2CH_2C_2H_5$

Figure 4. Synthesis of Substituted Glutamines.

ality during the sequence of reactions necessary for the desired transformation.

Since glutamines find much of their importance in peptide linkages, much of the recently studied chemistry of glutamine has concerned peptides containing glutamine as a component. Some glutamine derivatives, for example N-benzylglutamine, have been shown (14) to have an inhibitory effect on the growth of Streptococcus lactis, although this action does not occur with most glutamine derivatives.

One potentially useful series of glutamine derivatives appears to be sulfanilylglutamines, VII. These compounds, reported by Ose and Takamatsu (31), have been found to exhibit anti-virus activity and are useful in the treatment of Japanese encephalitis, infatile paralysis, and Newcastle disease in hens. These compounds were prepared by reacting p-nitrobenzenesulfonyl chloride with a suitable glutamine or glutamic acid derivative in 5 percent sodium hydroxide, followed by catalytic reduction of the nitro-group to give the corresponding sulfanilamide. Since none of the reported sulfanilylglutamines contained alkyl or aryl substituents on the amide nitrogen atoms, part of the work described in this thesis was oriented toward the development of a reasonable method of preparing N^5-substituted sulfanilylglutamines.



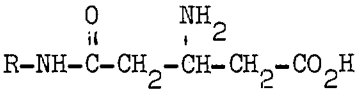
VIII

where R = H, alkyl, aryl.

Figure 5. Structure of Sulfanilylglutamines.

Figure 5 shows the general structure of these glutamine derivatives. Not unexpectedly, compounds of this type were found to be readily prepared by reaction of p-nitrobenzenesulfonyl chloride and the corresponding substituted glutamine, followed by catalytic hydrogenation of the nitro group to the amine.

A second class of glutamines which could be of interest are β-glutamines, shown in Figure 6. Prior to 1953, β-aminodicarboxylic acids were not mentioned in the chemical literature. Since that time,



IX

where R = H, alkyl, aryl

Figure 6. Structure of β-Glutamines.

a few syntheses of these compounds have been reported (4,7). In 1964 Khedouri et al. (27) reported the synthesis of β-glutamine from β-glutamic acid. At the present time the literature contains no reference pertaining to β-glutamine derivatives containing substituents on the amide nitrogen, or to the sulfonyl derivatives of β-glutamic acid or β-glutamines. The development of a synthetic pathway to these compounds was one objective of this work.

One problem associated with the preparation of β-glutamine derivatives in any appreciable quantity was a reasonable method of

preparing β-glutamic acid from readily available starting materials. Several groups (4,19) have reported the synthesis of β-aminodicarboxylic acids by reduction of substituted hydrazones of the corresponding β-keto esters, and Feuer and Swarts (16) have prepared β-glutamic acid by addition of ammonia to the activated double bond of diethyl glutaconate, followed by hydrolysis of the ester groups. These syntheses have several drawbacks, chiefly low yields and a fairly large number of steps involving difficult and time consuming operations. The problems associated with the synthesis of β-glutamic acid were decreased by development of the synthesis shown in Figure 7. The starting material, diethyl acetonedicarboxylate, X, is readily prepared from citric acid by methods previously described in the literature (2). The synthetic path shown has the advantage of being carried out without having to purify the product from any of the steps in the reaction sequence, thus saving considerable time and effort.

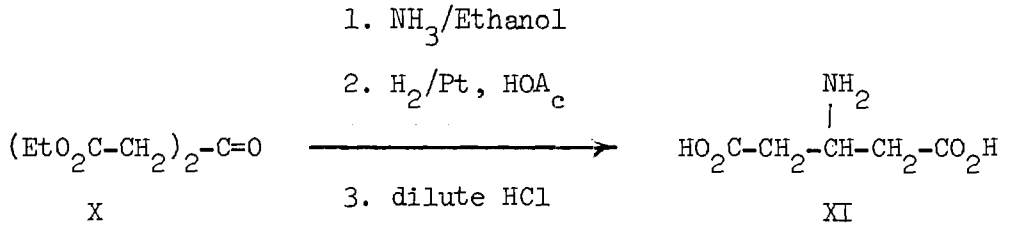


Figure 7. Preparation of β-Glutamic Acid.

Once a ready source of β-glutamic acid was available, the preparation of β-glutamines could be undertaken using methods similar to those employed for the preparation of glutamine derivatives, namely, protection of the amino group, formation of the cyclic anhydride,

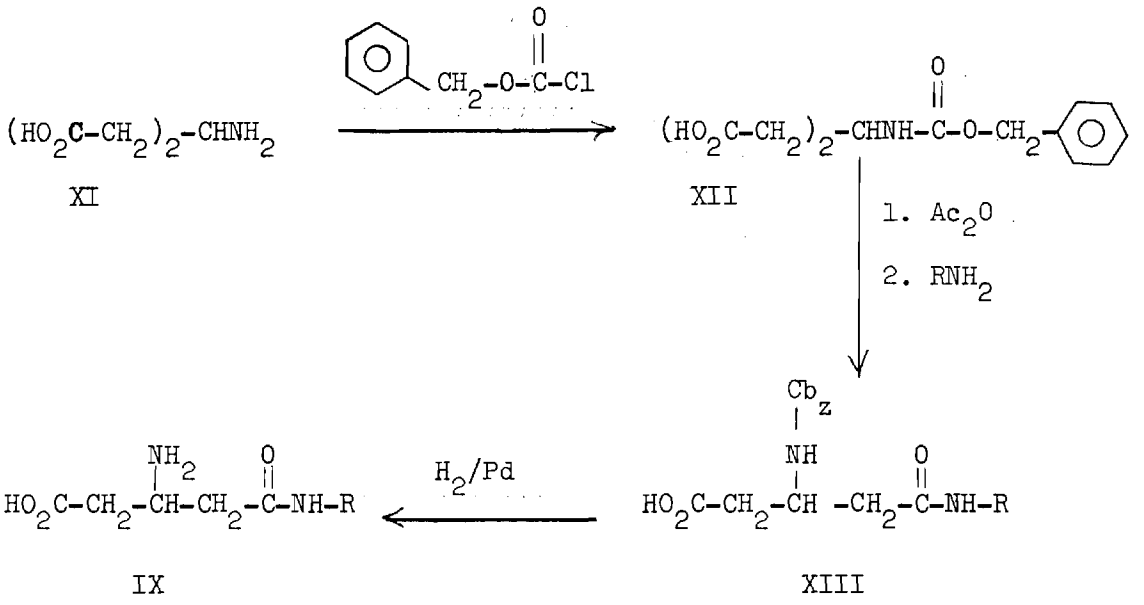


Figure 8. Preparation of β-Glutamine Derivatives.

reaction with a primary or secondary amine, and finally removal of the protective group on the amine. This sequence of reactions is shown in Figure 8. One fortunate aspect of the syntheses of β-glutamines is that due to the symmetrical structure of the anhydride, conversion of the cyclic anhydride to the amide can give only one product, instead of two products as is possible using glutamic anhydride. It should also be noted that the products of these reactions will be racemic mixtures, since the starting material was an optically inactive compound.

Synthesis of sulfanilyl derivatives of the β-glutamines should be effected by the method of Ose and Takamatsu (31), described previously. It would be of interest to compare the activity of the

sulfanilyl β-glutamine derivatives with the sulfanilyl glutamines previously reported. Also of interest would be the synthesis of sulfanilyl β-glutamic acid, using the method of Wagner and Wagner-Jauregg (47). The latter compound could be compared with sulfanilyl-glutamic acid as well as with the sulfanilyl glutamine and β-glutamine derivatives.

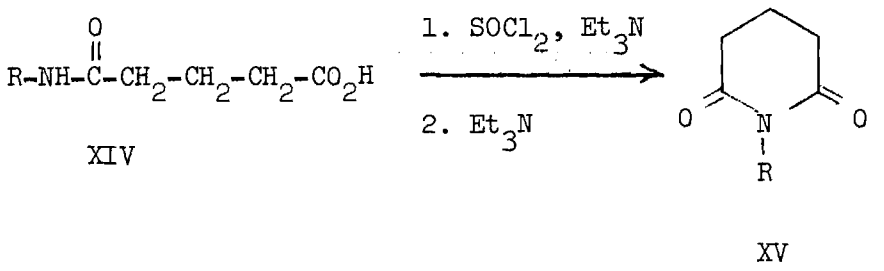
Glutarimides are compounds having the 2,8-dioxopiperidine structure shown previously in Figure 11. The first of these compounds was prepared before the turn of the present century. Since that time large numbers of glutarimides have been prepared by various workers. One series of glutarimides prepared in large numbers is the β,β-dialkyl glutarimides, prepared by the well known Guareschi synthesis described below. Also many N-substituted glutarimides are reported throughout the chemical literature. Some of the glutarimide derivatives reported in the current literature are connected to peptide chains and result from cyclization of the glutamine containing portion of such a chain. These syntheses are described in more detail below.

Prior to 1950, little attention had been given to the pharmacology of glutarimides, however the discovery of Shaw et al. (36) of the analeptic activity of β-ethyl-β-methyl-glutarimide ("Megimide") and its subsequent success as a barbiturate antagonist (37) led to studies of the pharmacology of a large number of glutarimide derivatives. In 1955, Tagmann, Sury and Hoffman (43,44) introduced α,α-phenylethylglutarimide ("Doriden") as a new class of sedative hypnotic, leading to further interest in glutarimides. Since this time

other groups have prepared many glutarimides having useful activity. Somers (38) has reported finding both analeptic and hypnotic activity in a series of β-alkyl-substituted glutarimides. The use of β,β-disubstituted glutarimide salts has been reported by Wiggins and Ablett (48) to reduce the recovery time from barbiturate anesthesia in both humans and animals. Other glutarimides have been used for treatment of motion sickness (10), and for their antihistiminic (10) properties. A series of aminoglutarimide derivatives, discussed in more detail below, have been found to exhibit anti-virus properties and have been used for the prevention and treatment of diseases caused by viruses.

Glutarimide derivatives may be prepared by a variety of methods. Early methods involved the heating of glutaronitrile and acetic acid in a sealed tube (35) or heating the ammonium salt of glutaric acid at 200° (6). The well known Guareschi synthesis (22,23), used for producing α,α-dicyano-β,β-dialkylglutarimides, involves the condensation of aliphatic ketones with cyanoacetic ester and ammonia. More recent procedures used in the preparation of glutarimides involve the reaction of sulfamide and glutaric acid in hot pyridine (28), cyclization of glutamine derivatives by refluxing in xylene (25), by heating in acetic anhydride (29), or by treatment of esters of glutamine derivatives with sodium alkoxide (39). One procedure which has been of importance in this work is that of Clayton, Kenner, and Shepherd (11), involving treatment of a glutamine derivative with one equivalent each of thionyl chloride and a tertiary amine, followed

by addition of one additional equivalent of base. This reaction is shown in Figure 9. From the previous literature descriptions and the



XIV

XV

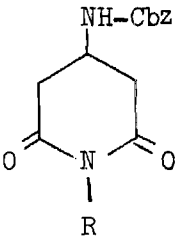
where R = H, alkyl, aryl, acyl

Figure 9. Preparation of Glutarimides.

results of the work reported in this thesis, this procedure appears to offer a general method of preparing glutarimide derivatives, almost regardless of the nature of the groups on the amide function of the molecule.

One series of glutarimide derivatives which appear to be of considerable interest are derivatives of α-aminoglutarimide. Several groups (30, 33) have prepared acylated derivatives of α-amino-glutarimide, either by cyclization of the corresponding acylglutamine derivatives of by reaction of α-aminoglutarimide with the appropriate acyl chloride. Most of the compounds thus prepared have been found to exhibit anti-virus activity and have potential use in treatment of virus-related diseases.

A goal of this research was to expand the scope and knowledge of aminoglutarimide derivatives by preparing new derivatives and devising general synthetic procedures for their preparation. In particular, it was desired to produce α-aminoglutarimide derivatives bearing alkyl or aryl substituents on the imide nitrogen, and to produce the analagous β-aminoglutarimide derivatives XVI for a comparison of properties. The structure of these latter compounds is shown in Figure 10.

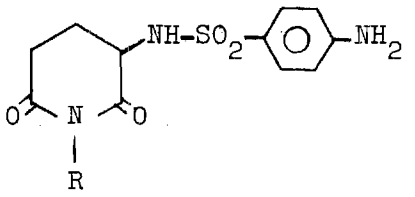


XVI

where R = H, alkyl, aryl; Cb^z = $-CO_2CH_2C_6H_5$

Figure 10. Structure of β-Aminoglutarimide Derivatives.

Another proposed synthesis of a glutarimide derivative involved preparation of α-sulfanilamidoglutarimides, whose structure is shown in Figure 11. Such compounds would be of interest for several reasons. Since many sulfanilamides possess useful activity against diseases of bacterial and protozoal origin, it would seem worthwhile to prepare a sulfanilamide derivative of a compound which had similar activity of its own. One could perhaps expect such a compound to exert a combined effect or possibility an effect which would be greater than



XVII

where R = H, alkyl, aryl

Figure 11. α-Sulfanilamidoglutarimides.

the effect the individual components alone could exert on the bacteria or virus causing a specific disease (synergistic effect). It would also be of interest to compare the pharmacology of the sulfanilamidoglutarimides to that of the sulfanilylglutamines reported in the literature and in this work.

As implied earlier, no references have appeared in the literature pertaining to β-aminoglutarimides, or to sulfanilamide derivatives of α-aminoglutarimides.

CHAPTER II

DISCUSSION OF EXPERIMENTAL INVESTIGATIONS

The pathway first proposed for the preparation of sulfanilamidoglutarimides was the preparation of a chloro- or bromoglutarimide, displacement of the halogen with ammonia, and reaction with p-nitrobenzenesulfonyl chloride followed by catalytic reduction of the nitro group. This proposed synthesis is shown in Figure 12 for the preparation of β-sulfanilamidoglutarimide. Unfortunately, all attempts to cyclize β-chloroglutaric acid, XX, to form β-chloroglutarimide, met with apparent failure, probably due to the lability of the β-chloro group in the presence of base. Cyclization methods which were investigated include heating the ammonium salt of β-chloroglutaric acid, heating the acid at 170° for four hours in formamide, and heating the acid with sulfamide in pyridine for three hours. In retrospect, this approach may have been somewhat naive when one considers the reactivity in elimination reactions of a halogen atom in a position beta to two carbonyl groups. Although no products of any of these reactions were isolated and identified, it would seem likely that the chlorine was lost from the β-chloroglutaric acid in a base catalyzed elimination reaction, as indicated by the lack of any C-Cl absorptions in the IR spectrum of the product. Further degradation may have occurred under the reaction conditions which prevailed.

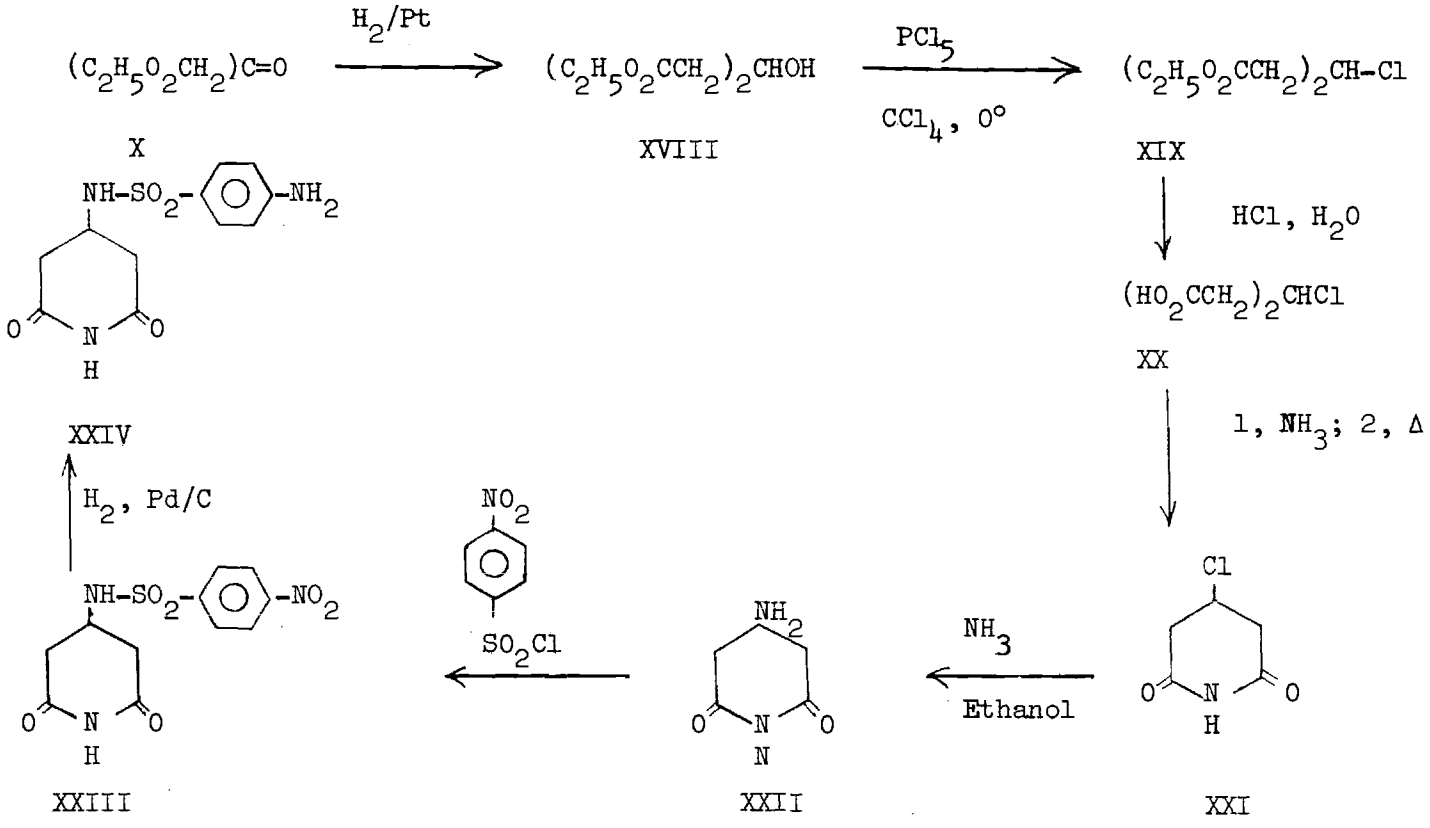


Figure 12. Synthesis of Sulfanilamidoglutarimides.

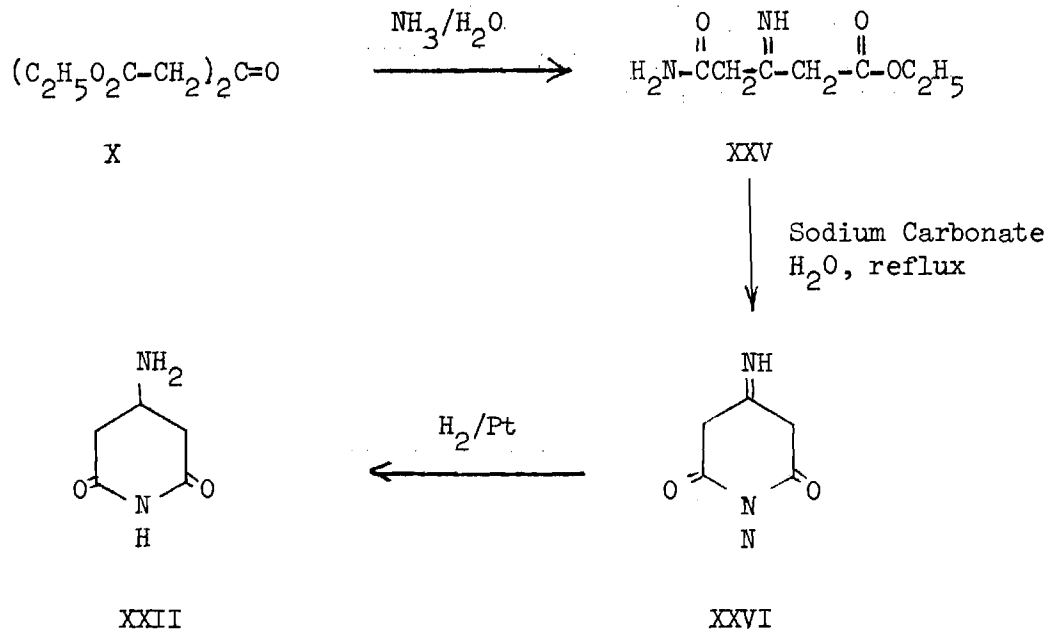


Figure 13. Alternate Synthesis of β-Aminoglutarimide.

A second approach to the preparation of β-aminoglutarimide, XXII, was the synthesis of β-iminoglutarimide, XXVI, followed by catalytic reduction of the imine group to the corresponding amine. This sequence of reactions necessary to effect this transformation is shown in Figure 13. The reduction of β-iminoglutarimide was made extremely difficult by the lack of solubility of the starting material in any common hydrogenation solvent. After several futile attempts to reduce the material using dimethylsulfoxide as the reaction solvent, the reaction scheme was abandoned.

At this point it was decided to prepare a specific sulfonamide derivative of an aminoglutarimide, namely, sulfanilyl α-aminoglutarimide, XXIV. It was hoped that this compound would serve as a model compound

for the determination of general spectral properties and solubilities of similar compounds. The synthesis shown in Figure 14 was not intended as a general pathway to sulfonamide derivatives of amino-glutarimides, although it could possibly be used if low yields are not objectionable to the experimenter. The preparation of p-nitro-benzenesulfonylglutamine, XXVI, is described in the literature (31) and was readily accomplished with no difficulty. Conversion of the glutamine derivative to the corresponding glutarimide by heating the material at 190° for 15 to 30 minutes was straightforward, however, the product which was formed in the reaction was highly discolored. Original efforts to decolorize the reaction mixture involved either refluxing a tetrahydrofuran solution of the product in the presence of activated Norite A or passing a solution of the reaction products through a chromatography column which had been packed with activated charcoal. Better yields of a less highly colored product were isolated in later reactions by decolorizing a refluxing tetrahydro-furan solution of the material with cocoanut charcoal. The best yields obtainable for the cyclization reaction using this method were on the order of 25 percent. While these yields are admittedly low, the method did allow preparation of the glutarimide derivative in sufficient quantities to continue the reaction sequence shown in Figure 14.

The catalytic reduction of the nitro group to the corresponding amine proceeded as expected to give the desired sulfanilamide deri-vative, with no unexpected side reactions. No unusual physical or

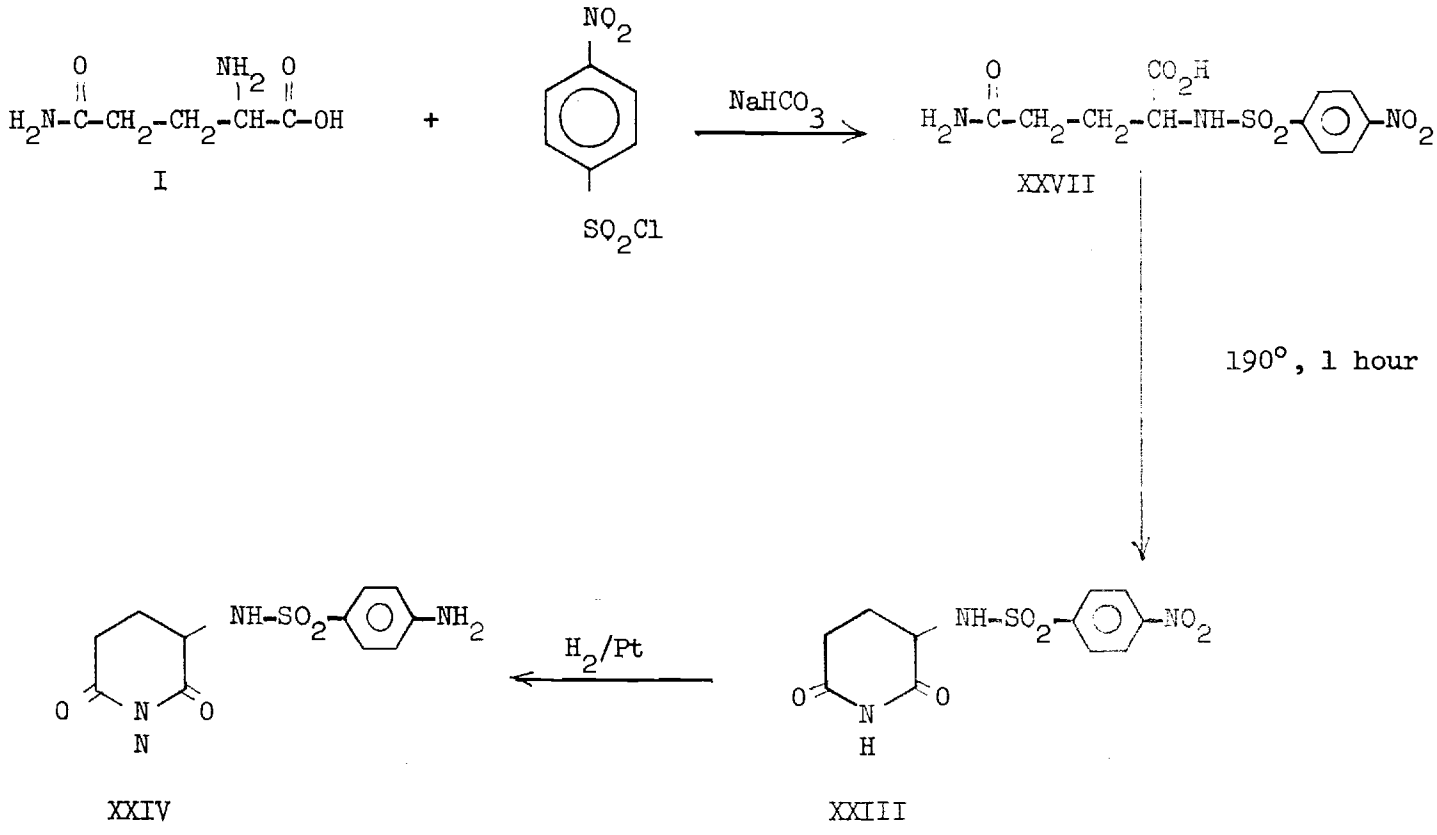


Figure 14. Synthesis of Sulfanilyl α-Aminoglutarimide.

spectral properties were found with the sulfanilyl-α-aminoglutarimide. An IR spectrum showed a carbonyl C=O absorption at 1680 cm^{-1} and sulfonamide S=O absorptions at 1145 and 1350 cm^{-1}. Prominent peaks in the mass spectrum included a molecular ion at 283 amu and a peak at 156 amu corresponding to cleavage of the sulfur-nitrogen bond in the sulfonamide group.

The reaction sequence shown in Figure 15 was found to give higher yields of p-nitrobenzenesulfonyl-α-aminoglutarimide, without the need for decolorizing the reaction product as described previously. The conversion of XXVIII to XXIV takes place when the sodium ethoxide abstracts a proton from the carboxamide, followed by an intramolecular displacement of ethoxide ion by the amide anion. This reaction was found not to occur in this particular instance unless two equivalents of ethoxide ion were used. The apparent reason for this observation is that the more acidic sulfonamide must be converted to its anionic form before the base can remove a proton from the carboxamide.

With the successful preparation of a relatively simple sulfanilyl derivative of an aminoglutarimide accomplished, attention was turned toward establishing a general synthesis of such compounds. The first efforts at such a synthesis involved the reaction of carbobenzoxyglutamic anhydride with an amine, followed by strong heating of the crude reaction product. This proposed synthesis is shown in Figure 16. When the amine used in this synthesis was benzylamine, several products were isolated by chromatography from the

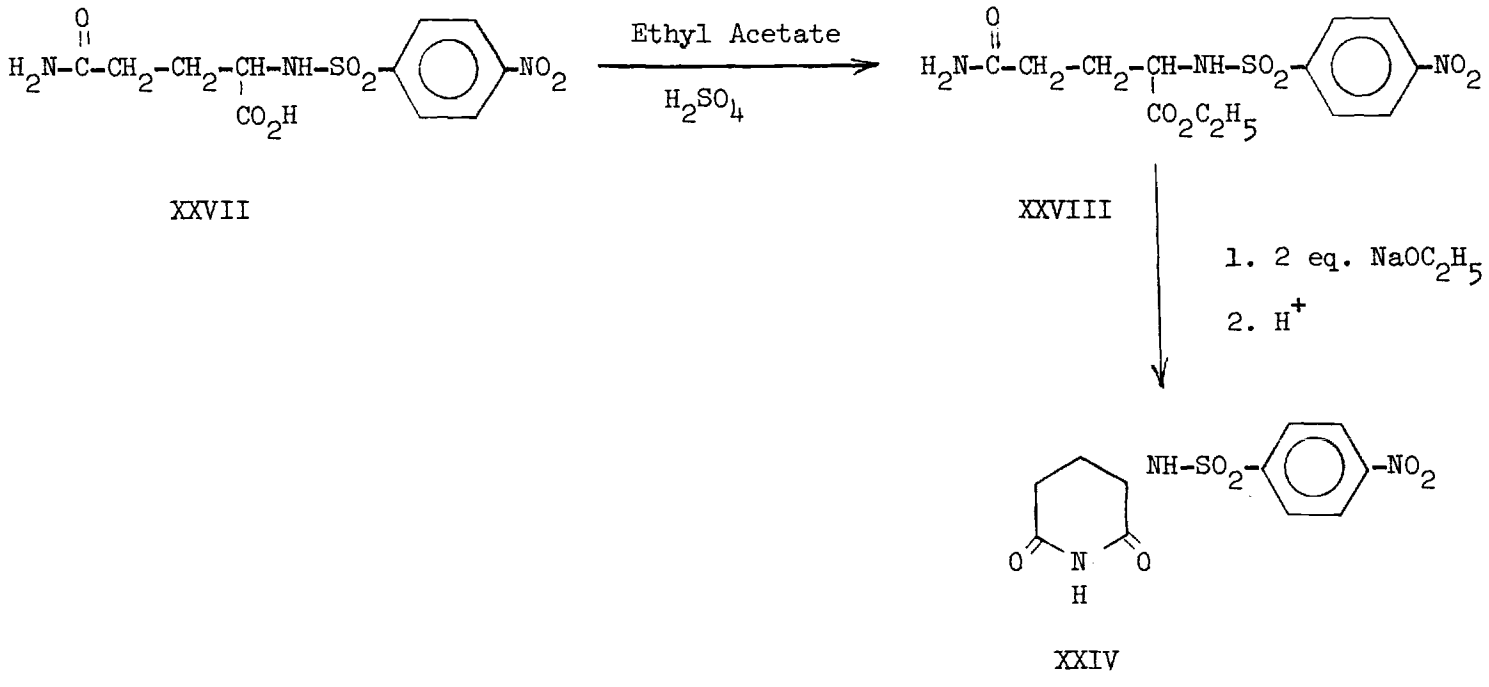
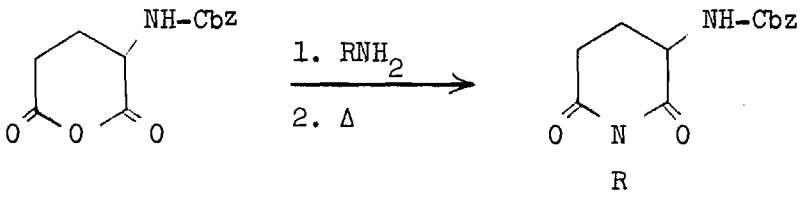


Figure 15. Alternate Synthesis of p-Nitrobenzene-sulfonyl-α-aminoglutarimide.

mixture of reaction products, but the desired glutarimide derivative was not among these products. The products which were identified were N,H-dibenzyl carbobenzoxyglutamide, N-benzyl pyroglutamide, and N,N-dibenzylcarbamoyl-2-pyrrolidinone. Formation of the last compound is interesting since it could only be formed if the benzylamine displaced benzyl alcohol from the carbobenzoxy group originally present. Whether the displacement occurred before or after the cyclization reaction had taken place cannot be determined from the available data.

Also of interest is the observation that the cyclic materials which were isolated contained five membered rings instead of the desired six membered rings. These compounds could arise only if the



V XXIX

where R = alkyl, aryl; Cbz = $-CO-CH_2C_6H_5$

Figure 16. First Attempted Synthesis of Substituted α-carbobenzoxyaminoglutarimides.

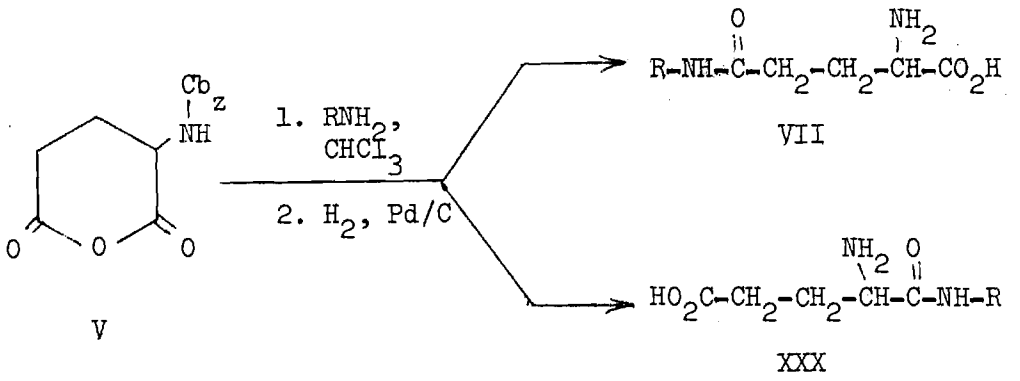
amine reacts with the cyclic anhydrive V at the carbonyl group adjacent to the carbobenzoxyamino substituent. The ring size of the pyrrolidinone derivative was deduced from its IR spectra, which contained carbonyl absorptions at 1635, 1700 and 1765 cm^{-1}. Dyer (13)

has reported that cyclic five-membered imides are expected to have a carbonyl absorption in the vicinity of 1770 cm^{-1}, whereas cyclic six-membered imides have carbonyl absorptions at 1700 and 1710 cm^{-1}.

Since it seemed desirable to isolate and purify the reaction product of the carbobenzoxyglutamic anhydride and an amine, reaction conditions were modified to give such a result. Edelson, Skinner and Shive (14) have reported the synthesis of a series of carbobenzoxyglutamines by the reaction of an amine with carbobenzoxyglutamic anhydride in an ethanol-benzene solvent.

When the synthesis of N-phenyl and N-benzyl carbobenzoxyglutamine was repeated in this work, the melting points of the products obtained differed from those reported by the above group. The melting points of the corresponding glutamine derivatives also differed from the previously reported values. Changing the reaction solvent to chloroform gave the same products, although the reaction work-up was simplified.

Since elemental analyses of the above products gave the correct values for the desired structures, an investigation was undertaken into the α-amino acid content of the substituted glutamine derivatives. It was felt that such an investigation would indicate which of the two possible isomers shown in Figure 17 was actually formed. If the reaction products were the isoglutamine derivatives, XXX, the melting points of the materials prepared in this work might be expected to differ from the glutamine derivatives, VII, reported



where R = alkyl, aryl; Cb_z = $-CO_2CH_2C_6H_5$

Figure 17. Reaction of Carbobenzoxyglutamic Anhydride and an Amine.

by Edelson, Skinner and Shive. The structure of the glutamines reported by Edelson et al. was determined by a quantitative ninhydrin reaction evolving carbon dioxide.

The method selected to determine the α-amino acid content of the products was that of Spies (40). This method is based upon the fact that two molecules of an α-amino acid XXXI and one cupric ion interact stoichiometrically with a concommitant deepening of the blue color of the solution due to the formation of the blue-colored amino acid-copper complex, XXXII, shown in Figure 18.

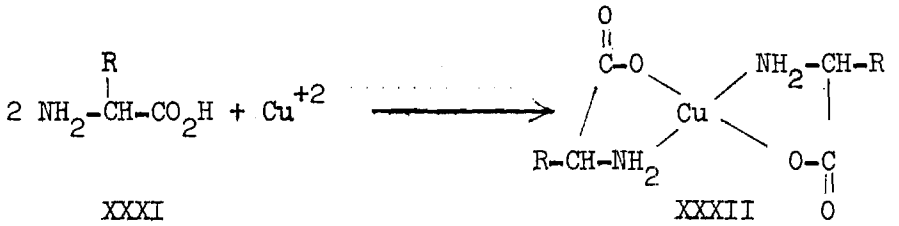


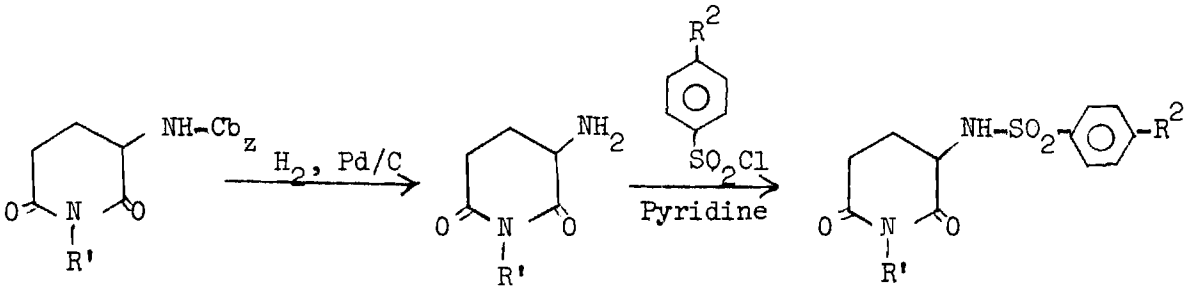
Figure 18. Formation of Amino Acid-Copper Complexes.

A standard curve was prepared by plotting the log percent transmittance at 230 mμ of an alanine-Copper complex versus the micromolar alanine concentration. This plot gave a linear relationship in the alanine concentration range of zero to 500 micromolar. Several glutamine and glutamic acid solutions were prepared and tested as above. The log percent transmittance of the complex at a given cencentration was found to correspond closely to that obtained using the standard curve. On the other hand, solutions of 4-aminobutyric acid, 6-aminocaproic acid, and 4-aminobenzoic acid gave results corresponding to zero α-amino acid content.

The results of Spies indicate that a glutamine derivative should form a complex with cupric ion whereas an isoglutamine derivative should not. Experimental results indicated that when aniline is reacted with carbobenzoxyglutamic anhydride in chloroform, an isoglutamine derivative is formed, and when the reacting amine is benzylamine, a mixture of the glutamine and isoglutamine derivatives was formed. Such an observation would result if the more basic benzylamine was affected by steric and electronic factors while the less basic aniline was more affected by electronic factors in their reaction with the anhydride.

With the isolation and characterization of the glutamine derivatives completed, attention was focused on methods of cyclizing the materials. Carbobenzoxyglutamine itself was easily cyclized to the imide by heating at 190° for 30 minutes. No attempts were made to observe the optical purity of the product in this work. The product

was easily converted to α-(N-acetyl)sulfanilamidoglutarimide by hydrogenolysis of the carbobenzoxy group, followed by reaction with N-acetylsulfanilyl chloride in pyridine. This compound was identical to the product which was prepared by heating N-acetylsulfanilyl-glutamine at 190° for 30 minutes. It would appear that, in general, sulfonamide derivatives of aminoglutarimides, such as XXXIII, could be prepared from carbobenzoxyaminoglutarimides by the scheme shown in Figure 19.



Where R' = H, alkyl, aryl; R^2 = alkyl, $-NO_2$, $-NHCOCH_3$

Figure 19. Preparation of Sulfonylamidoglutarimides.

The preparation of substituted carbobenzoxyaminoglutarimides was more problematical than expected. As shown in Figure 20, the cyclization of carbobenzoxyisoglutamines XXXV can give two possible isomeric compounds, containing either a five-membered ring (XXXVI) or a six-membered ring (XXXVII). It is a well known fact that five-membered rings containing exocyclic double bonds are more stable than their six-membered analogs. This observation leads to the conclusion that XXXVI should be formed in preference to XXXVII in the cyclization

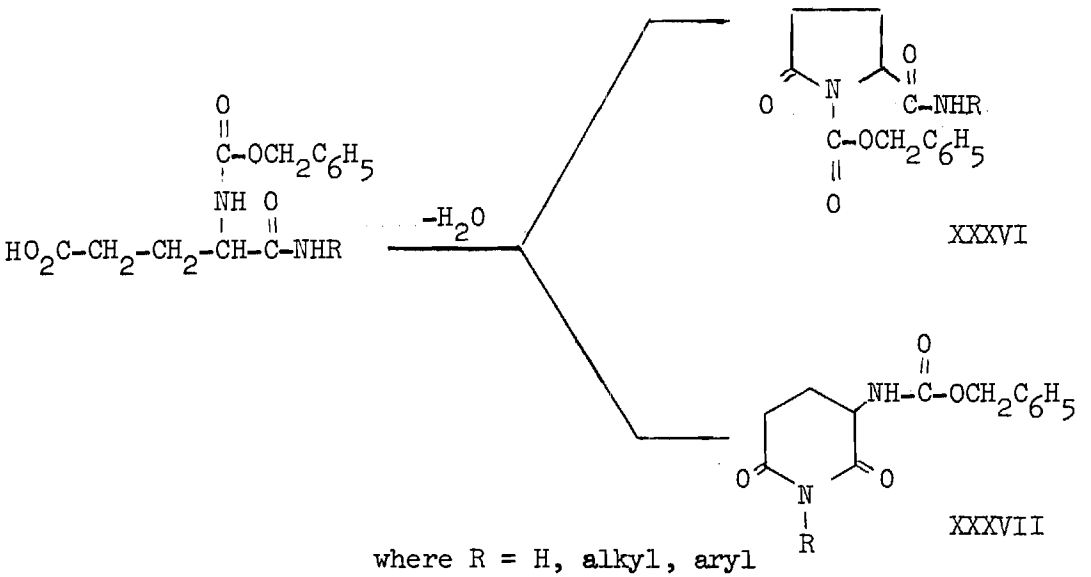


Figure 20. Cyclization of Carbobenzoxyisoglutamines.

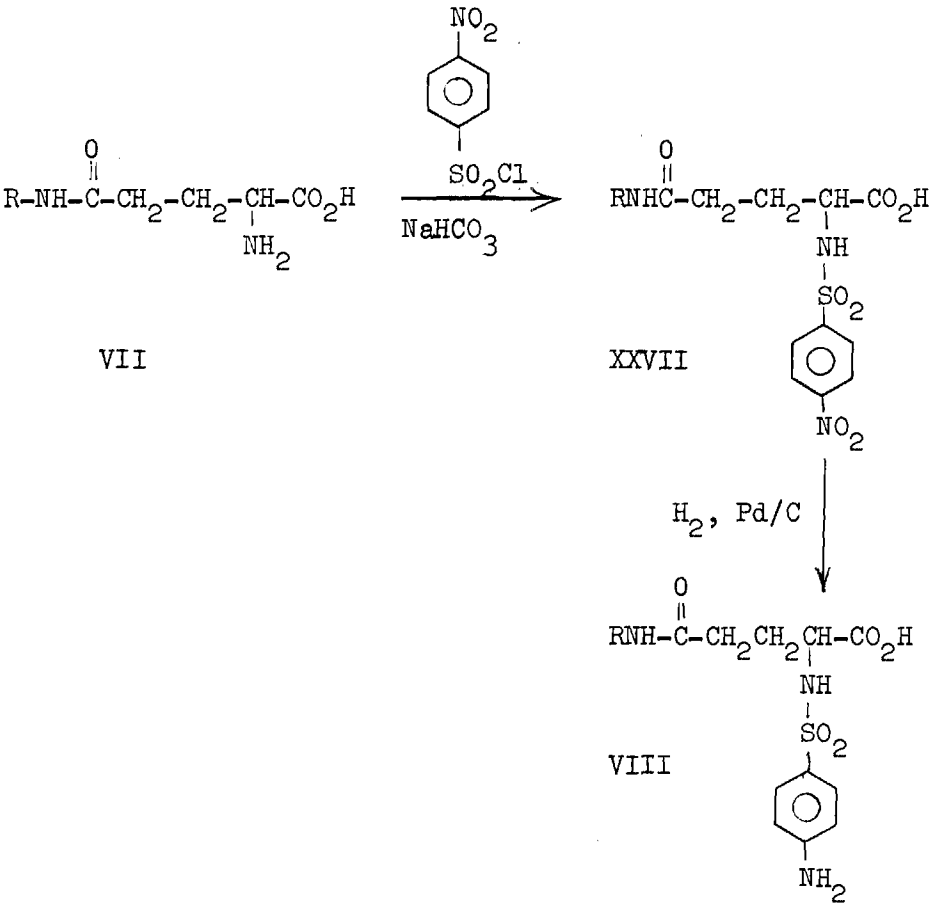
shown in Figure 20.

When the mixture of N-benzyl carbobenzoxyglutamine and N-benzyl carbobenzoxyisoglutamine was subjected to cyclization conditions, a product was formed whose elemental analysis indicated loss of a water molecule from the starting material. This produce was determined to contain a five-membered ring from spectral data. The carbobenzoxy group generally has a carbonyl C=O absorption at 1680 cm^{-1}. A six-membered cyclic imide is reported to have carbonyl absorptions at 1700, 1710 cm^{-1}, while cyclic five-membered imides have carbonyl absorptions at 1700 and 1770 cm^{-1} (13). Additionally, the amide group in a structure such as XXXVI should have a carbonyl absorption in the range of 1680-1630 cm^{-1}. An IR spectrum of the product contained absorptions at 1770 and 1680 cm^{-1}, in agreement with the expected absorptions for the five-membered system. Strong support

was given to the assigned structure by the NMR spectrum of the product, which contained a two proton doublet at 5.6τ. This doublet could arise only if the methylene protons of the benzyl group attached to nitrogen were split by a proton on the same nitrogen. Such splitting is possible only in a five-membered imide such as XXXVI. This it appears that the desired glutarimide derivative was not formed in any of the reactions which yielded a product of the desired elemental analysis.

Attempts to cyclize N-phenyl carbobenzoxyisoglutamine failed to give any products whose analyses or spectra indicated the loss of a water molecule. Several products which appeared to be the result of a more complex reaction were isolated and purified, but none were conclusively identified. Further efforts to prepare aminoglutarimide derivatives were directed exclusively to the β-aminoglutarimides when the above work was completed unsuccessfully.

The conversion of the N^5-substituted glutamines to the corresponding sulfanilylglutamine derivatives was attempted by the method shown in Figure 21. Each of the indicated steps in the reaction sequence was readily effected. Yields from the reaction of the glutamine derivatives and p-nitrobenzenesulfonyl chloride were somewhat lower than the yields reported for the reaction of glutamine and the sulfonyl chloride. However, little work was done to maximize the reaction yields, and it is quite likely that conditions utilizing greater quantities of reactants and better recrystallization techniques would lead to higher product yields. Extremely good yields

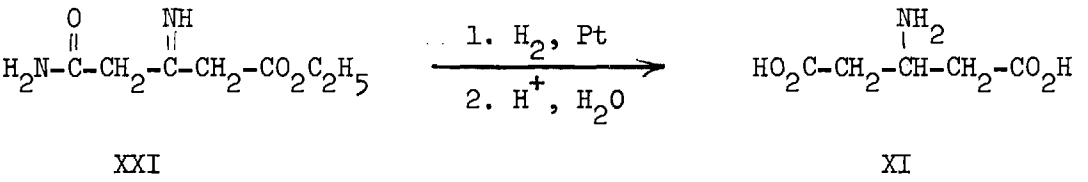


where R = H, alkyl, aryl

Figure 21. Synthesis of Sulfanilylglutamines.

were obtained in the conversion of the nitro group to the corresponding amine in the last step of the synthesis.

With the synthesis of the above sulfanilamide derivatives completed, attention was directed toward the preparation of β-glutamine derivatives and β-aminoglutarimide derivatives. Development of a good synthesis of β-glutamic acid was necessary before this work could be begun. Early attempts to reduce compound XXV in Figure 22 followed by acid hydrolysis of the amide and ester groups



XXI XI

Figure 22. First Proposed Synthesis of β-Glutamic Acid.

met with failure and had to be abandoned. β-glutamic acid was finally prepared in reasonably good yields by the procedures shown in Figure 23. The reactions involved in this synthesis have the advantage of being quite easy to perform and it is not necessary to purify the product after each step of the synthesis. These factors could make this method of preparation more practical than procedures involving the reduction of hydrazone derivatives of diethyl acetonedicarboxylate or the amination of diethyl glutaconate which have been proposed by other groups (16, 19) for the synthesis of β-glutamic acid.

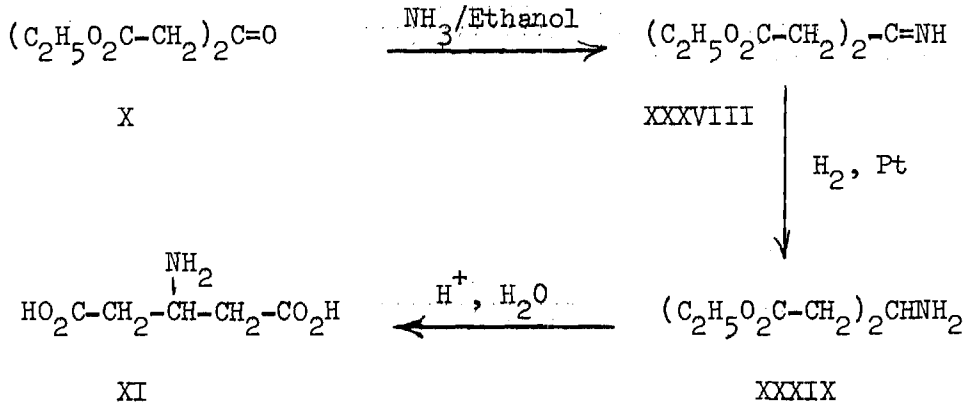
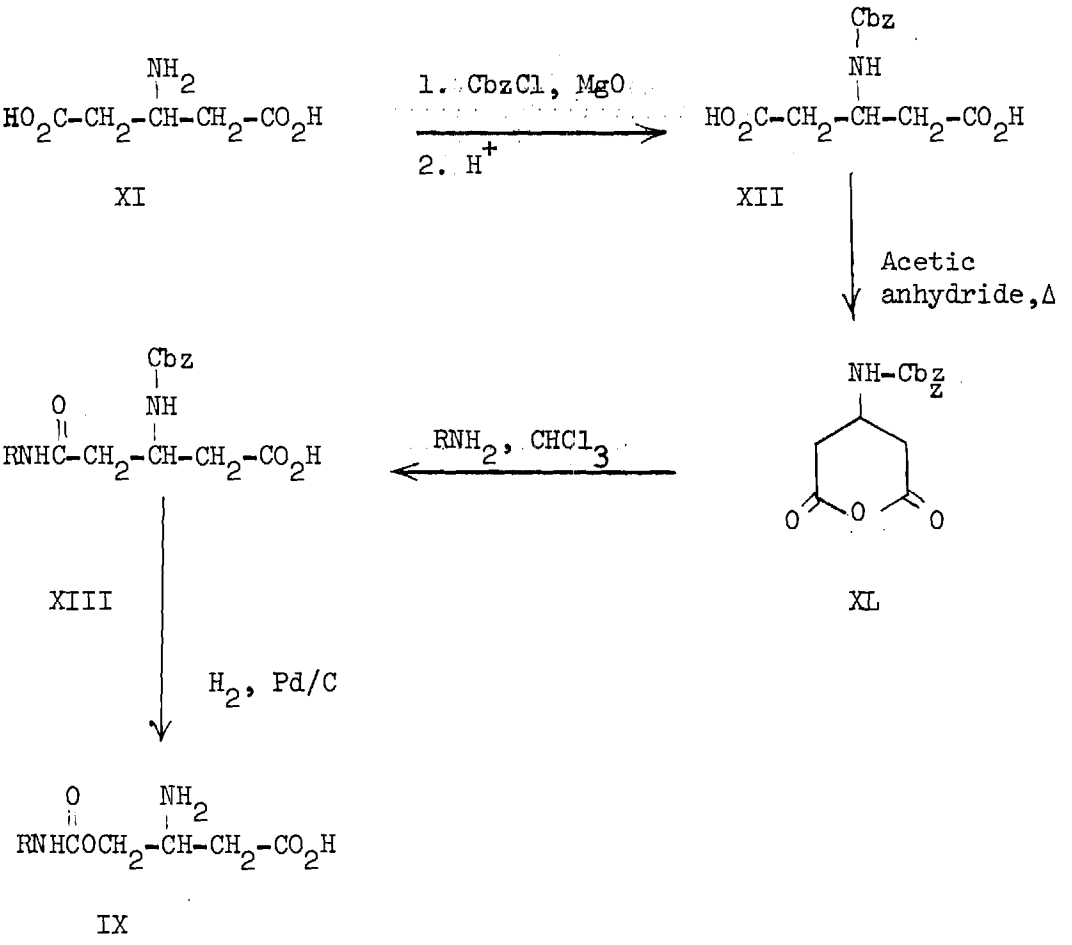


Figure 23. Preparation of β-Glutamic Acid.

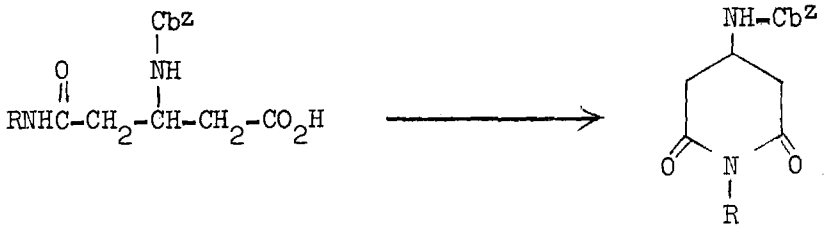
The general method of preparing β-glutamine derivatives, shown in Figure 24, was quite similar to the procedure used for the preparation of substituted glutamines shown in Figure 17. One factor which makes the synthesis of the β-glutamines relatively simple is that only one product can result from the reaction of an amine and carbobenzoxy-β-glutamic anhydride due to the symmetrical nature of the latter compound. β-glutamine, as well as N-benzyl- and N-propyl-β-glutamine were easily prepared by this method. No attempts were made to isolate the anhydride XI during any of these syntheses, although the other compounds shown in Figure 24 were isolated and characterized.

Several methods of preparing carbobenzoxy-β-aminoglutarimides were investigated. To synthesize these, it was necessary to find conditions which would give rise to the cyclization reaction shown in Figure 25. The most successful method found to effect this trans-



where R = H, alkyl, aryl; Cbz = $-CO_2CH_2C_6H_5$

Figure 24. Synthesis of β-Glutamines.



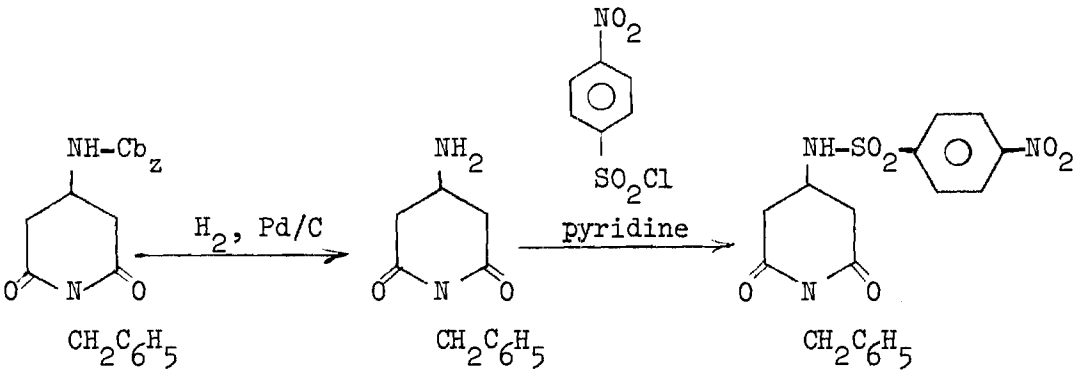
XIII XVI

where R = H, alkyl, aryl; Cbz = $-CO_2CH_2C_6H_5$

Figure 25. Preparation of Carbobenzoxy-β-aminoglutarimides.

formation was to treat the carbobenzoxy-β-glutamine derivative with one equivalent each of thionyl chloride and a tertiary amine, followed by the addition of a second equivalent of amine after 15 minutes. Although the reaction yields reported in this work are somewhat low, it seems very likely that once the characteristics of these compounds are known the reaction and work-up procedures could be modified to increase greatly the yields. Some preliminary work has indicated, for instance, that methanol may be a much better recrystallization solvent for these compounds than the ethanol-hexane mixture described in the experimental section of this work. It should also be noted that the reported yields of carbobenzoxy-β-aminoglutarimide derivatives are yields of analytical quality material and thus are lower than the yields expected from less stringent purification procedures. Each of these compounds was synthesized only once or twice, and the optimization of yields was not the major objective of the reactions.

To help establish a general preparation of sulfanilamido-glutarimides, N-benzyl β-carbobenzoxyaminoglutarimide was converted to the corresponding p-nitrobenzenesulfonyl derivative as shown in Figure 26. The N-benzyl β-aminoglutarimide XLII was not purified



XLI XLII XLIII

where R = H, alkyl, aryl; Cb_z = $-CO_2CH_2C_6H_5$

Figure 26. Preparation of N-Benzyl β-(4-Nitro-benzenesulfonamido)-glutarimide.

during the reaction sequence. The crude XLII gradually changed from a colorless oil to a dark blue oil upon exposure to air. The IR spectra of the free amine and the carbobenzoxy amine XLI were virtually identical in the range of usual carbonyl absorptions, although important differences were noted in the areas usually associated with N-H stretching and bending absorptions. In particular, the structure of the free amine was strongly supported by the absence of an IR absorption at 1540 cm^{-1} attributable to the N-H bending of the amide present in the starting carbobenzoxy derivative XXXVII.

It is felt that this work, coupled with the previously discussed

synthesis of N-acetylsulfanilyl-α-aminoglutarimide, proves that sulfonamide derivatives of aminoglutarimides can be easily prepared by hydrogenolysis of a carbobenzoxyaminoglutarimide followed by reaction of the ensuing product with a sulfonyl chloride in pyridine. Problems associated with the reaction of sulfonyl chlorides and 5-aminobarbituric acid derivatives, discussed elsewhere in this thesis, do not appear to occur with aminoglutarimide derivatives.

Although no attempts were made to produce sulfanilyl derivatives of β-aminoglutarimides, their synthesis should be readily possible by reduction of the nitro group of the corresponding p-nitrobenzenesulfonyl derivatives. Such a reaction was utilized earlier in this work for the preparation of sulfanilyl-α-aminoglutarimide. Results of this investigation would certainly appear to indicate the desired goal of developing a general method of synthesis of sulfanilyl aminoglutarimide derivatives.

Sulfanilyl-β-glutamic acid, XLIV, was prepared by the method shown in Figure 27. This procedure is identical to that used by Wagner and Wagner-Jaureg (47) for the preparation of sulfanilylglutamic acid, and no problems were expected or encountered. A comparison of the pharmacological properties of the two isomers could be of interest in relating the structure and activity of a given series of compounds.

A brief attempt to prepare sulfanilyl derivatives of β-glutamines was also undertaken. This work was halted when the β-glutamines themselves turned out to be insoluble in pyridine. Due to a lack of

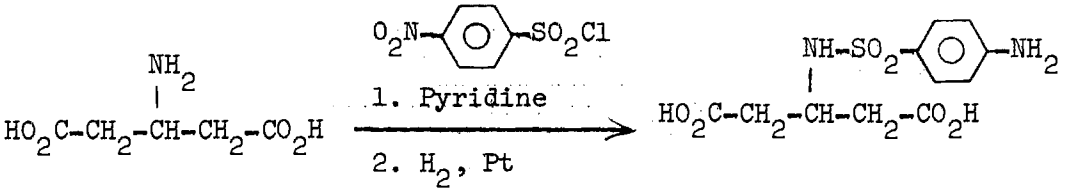


Figure 27. Preparation of Sulfanilyl-β-Glutamic Acid.

reactants, no efforts were made to effect the synthesis in sodium bicarbonate solutions, a method used by Ose and Takamatsu (31) for preparing sulfanilylglutamine, due to lack of available reactants.

In Table I are summarized all of the previously unreported compounds which were obtained during this investigation. IR spectra of most of many of these compounds are summarized in Tables 2, 3, and 4.

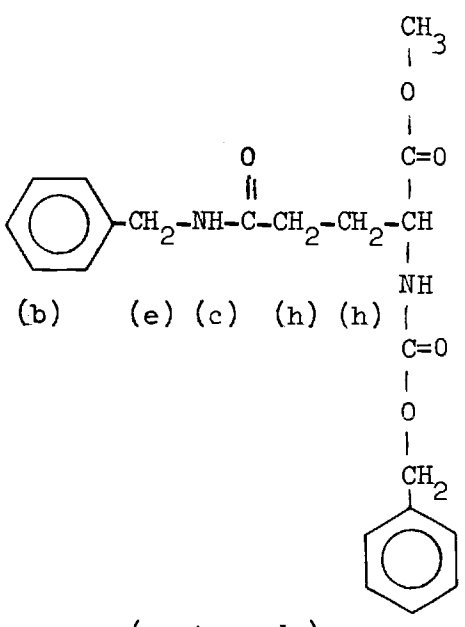
Table 1. New Compounds

Compound	M.P.(C°)
Diethyl Acetonedicarboxylate Tosylhydrazone	88-89
N-Benzyl Carbobenzoxyglutamine Methyl Ester	114-115
N-Phenyl Carbobenzoxyisoglutamine	193-194
N-Phenyl Isoglutamine	175-176
N-Benzyl Carbobenzoxy-β-glutamine	148-149
N-Propyl Carbobenzoxy-β-glutamine	178-179
N-Propyl Carbobenzoxy-β-glutamine Methyl Ester	125-126
N-Benzyl β-Glutamine	207-208
N-Propyl β-Glutamine	204-205
β-Glutamine Ethyl Ester Acetate Salt	67-69
1-Carbobenzoxy-5-(N-benzylcarboxamido)-2-pyrrolidinone	140-141
N-Phenyl Isoglutamine	175-176
N,N'-Dibenzyl Carbobenzoxyglutamide	213-214
β-Carbobenzoxyaminoglutarimide	125-126
N-Propyl β-Carbobenzoxyaminoglutarimide	90-91
N-Benzyl β-Carbobenzoxyaminoglutarimide	105-106
N-(p-Nitrobenzenesulfonyl)glutamine Ethyl Ester	169-170
N^2-(N-Acetylsulfanilyl)glutamine	185-186
N^5-Benzyl N^2-(p-Nitrobenzenesulfonyl)glutamine	217-218
N-Phenyl N-(p-Nitrobenzenesulfonyl)isoglutamine	192-193

Table 1. (Continued)

Compound	M.P.(C°)
p-Nitrobenzenesulfonyl-β-glutamic Acid	204-205
α-(p-Nitrobenzenesulfonylamido)-glutarimide	234-240
α-(N-Acetylsulfanilamido)-glutarimide	270-271
N-Benzyl β-(p-Nitrobenzenesulfonylamido)-glutarimide	219-220
N-Benzyl Sulfanilylglutamine	168-169
N-Phenyl Sulfanilylisoglutamine	177-178
Sulfanilyl β-Glutamic Acid	202-203
Sulfanilyl α-Aminoglutarimide	199-200

Table 2. NMR Shift Values in Units of δ for Derivatives of Glutamine.

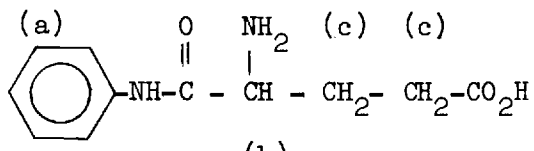


(b) (e) (c) (h) (h)

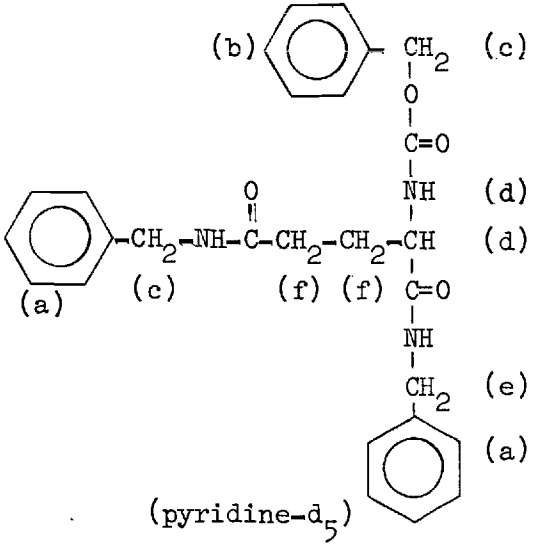
(acetone-d_6)

	(a)	(b)	(c)	(d)
	7.0	6.9	6.0	4.8
(f)	(g)			
	(e)	(f)	(g)	(h)
(d)	4.0	3.3	2.5	2.0
(a)	(doublet, 2H)	(singlet, 3H)	(singlet, 1H)	(multiplet, 4H)
(g)	(singlet, 5H)	(singlet, 5H)	(broad, 1H)	(singlet, 2H)

Table 2. (Continued)



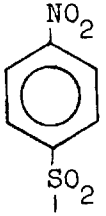
(a)	(b)	(c)
7.5	4.3	2.4
(singlet, 5H)	(multiplet, 1H)	(multiplet, 4H)



(a)	(b)	(c)
6.5	6.4	4.4
(singlet, 10H)	(singlet, 5H)	(singlet, 2H)

(d)	(e)	(f)
4.1	3.8	1.9
(broad, 2H)	(miltiplet, 4H)	(broad, 4H)

Table 2. (Continued).



(b)

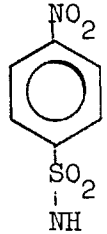
(a)

$H_2N-\overset{O}{\overset{\|}{C}}-CH_2-CH_2-\underset{(a)}{\overset{SO_2-NH}{\overset{|}{\underset{|}{CH}}}}-CO_2H$

(a) (d) (d) (c)

(pyridine-d_5)

(b)	(a)	(b)	(c)	(d)
	8.8	7.4	3.8	1.8
	(broad, 3H)	(singlet, 4H)	(multiplet, 1H)	(multiplet, 4H)



(a)

$H_2N-\overset{O}{\overset{\|}{C}}-CH_2-CH_2-\underset{(b)}{\overset{SO_2-NH}{\overset{|}{\underset{|}{CH}}}}-CO_2CH_2-CH_3$

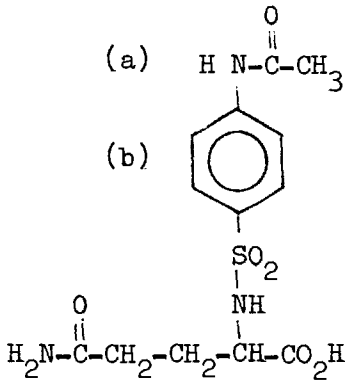
(d) (e) (e) (c) (c) (f)

(acetone-d_6)

(a)	(a)	(b)	(c)	(d)
	7.7	7.0	3.3	2.1
	(quartet, 4H)	(broad, 1H)	(multiplet, 3H)	(singlet, 2H)

(e)	(f)
1.6	0.4
(multiplet, 4H)	(triplet, 3H)

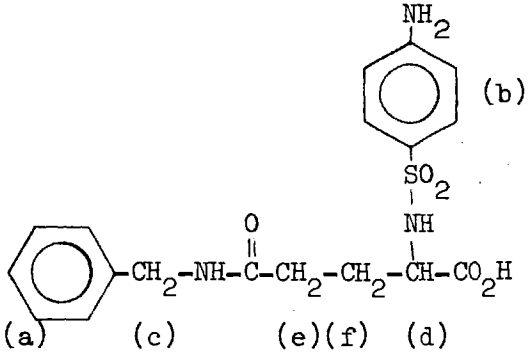
Table 2. (Continued).



(pyridine-d_5)

(a)	(b)	(c)	(d)
10.8	8.0	4.6	2.8
(singlet, 1H)	(singlet, 4H)	(broad, 1H)	(multiplet, 4H)

(e)
2.2
(singlet, 3H)

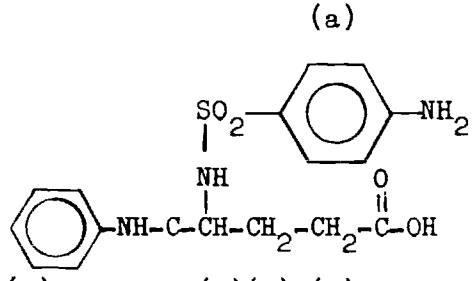


(acetone-d_6)

(a)	(b)	(c)	(d)
7.3	7.2	4.4	4.0
(singlet, 5H)	(quartet, 4H)	(singlet, 2H)	(broad, 1H)

(e)	(f)
2.4	1.9
(multiplet, 2H)	(multiplet, 2H)

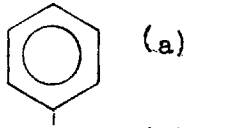
Table 2. (Continued).



(acetone-d_6)

(a)	(b)	(c)	(d)
7.3	4.0	2.5	2.0
(multiplet, (H)	(multiplet, 1H)	(multiplet, 2H)	(multiplet,2H)

Table 3. NMR Shift Values in Units of δ for Derivatives of β-Glutamic Acid.



(a)

(b)

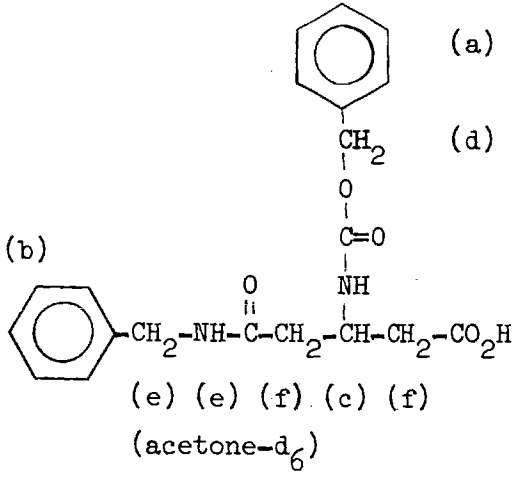
$HO_2C-CH_2-CH-CH_2-CO_2H$

(d) (c)(d)

(acetone-d_6)

(a)	(b)	(c)
7.4 (singlet, 5H)	5.1 (singlet, 2H)	4.4 (triplet, 1H)
(d)	(e)	(f)
2.7 (doublet, 4H)		

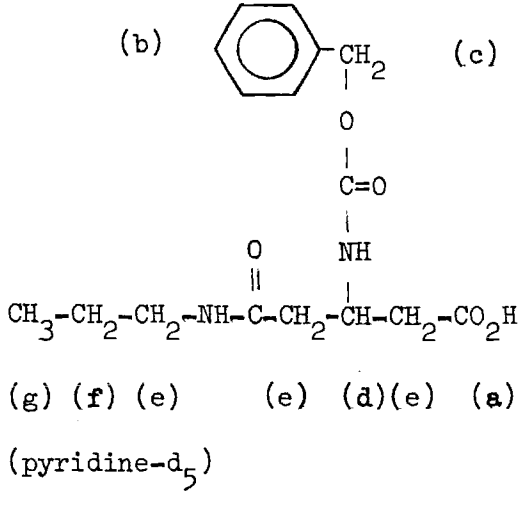
Table 3. (Continued).



(a)	(b)	(c)
7.4	7.3	6.5
(singlet, 5H)	(singlet, 5H)	(broad, 1H)

(d)	(e)	(f)
5.1	4.4	2.7
(singlet, 2H)	(multiplet, 3H)	(multiplet, 4H)

Table 3. (Continued).

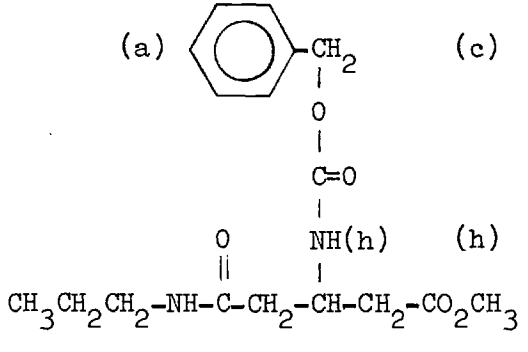


(a)	(b)	(c)
12.4	7.4	5.3
(singlet, 1H)	(multiplet, 5H)	(singlet, 2H)

(d)	(e)	(f)
5.0	3.2	1.5
(multiplet, 1H)	(multiplet, 6H)	(multiplet, 2H)

(g)
0.9
(triplet, 3H)

Table 3. (Continued).



(a)	(b)	(c)
7.4	6.2	5.2
(singlet, 5H)	(multiplet, 2H)	(singlet, 2H)
(d)	(e)	(f)
4.3	3.7	3.2
(multiplet, 1H)	(singlet, 3H)	(multiplet, 2H)
(g)	(h)	(i)
2.6	1.5	0.9
(multiplet 4H)	(multiplet, 2H)	(triplet, 3H)

Table 3. (Continued).

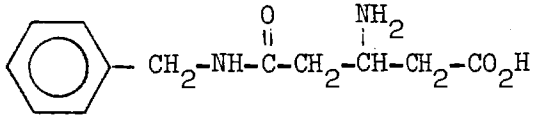
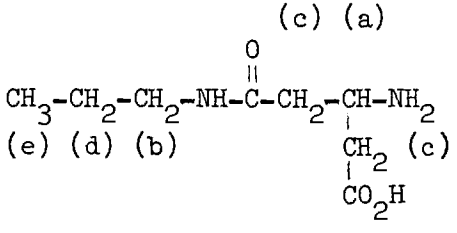
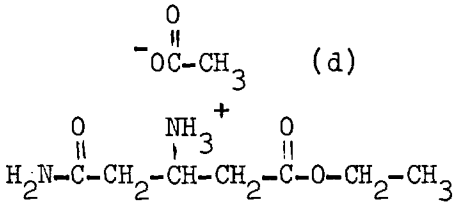
 (a) (b) (d) (c)(d) (CF_3CO_2H)	(a) 7.4 (singlet, 5H)	(b) 4.5 (doublet, 2H)	(c) 4.3 (broad, 1H)
	(d) 3.0 (multiplet, 4H)		
 (c) (a) (e) (d) (b) (D_2O)	(a) 3.8 (multiplet, 1H)	(b) 3.2 (triplet, 3H)	(c) 2.6 (multiplet, 4H)
	(d) 1.5 (multiplet, 2H)	(e) 0.9 (triplet, 3H)	

Table 3. (Continued).

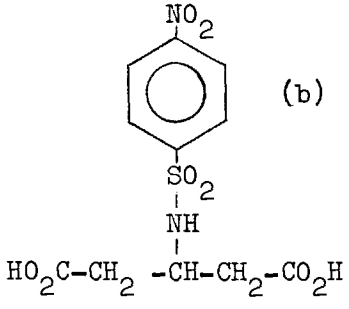


(c)(b) (c) (a) (e)

(acetone-d_6)

(a)	(b)	(c)
3.5	2.9	1.9
(quartet, 2H)	(multiplet, 1H)	(doublet, 4H)

(d)	(e)	(f)
1.3	0.6	
(singlet, 3H)	(triplet, 3H)	

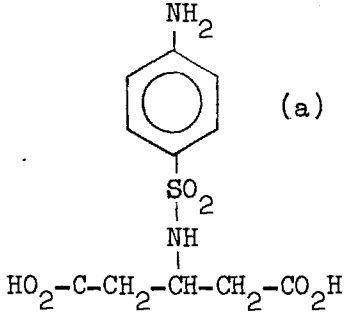


(d) (c)(d)

(dimethylsulfoxide-d_6)

(a)	(b)	(c)	(d)
10.0	8.4	4.0	2.6
(broad, 1H)	(quartet, 4H)	(broad, 1H)	(doublet, 4H)

Table 3. (Continued).



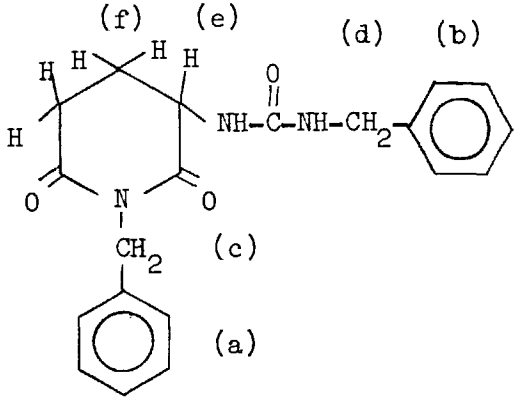
(a)

(c) (b)(c)

(acetone-d_6)

(a)	(b)	(c)
7.3	4.0	2.7
(quartet, 4H)	(triplet, 1H)	(doublet, 4H)

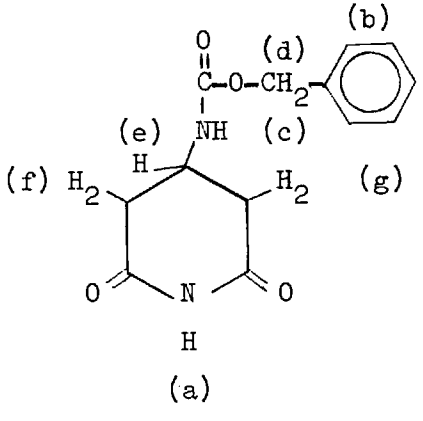
Table 4. NMR Shift Values in Units of δ for Derivatives of Glutarimide.



(pyridine-d_5)

(a)	(b)	(c)
6.5	6.4	4.0
(doublet, 5H)	(doublet, 5H)	(singlet, 2H)

(d)	(e)	(f)
3.8	3.6	1.8
(doublet, 2H)	(multiplet, 1H)	(broad multiplet, 4H)

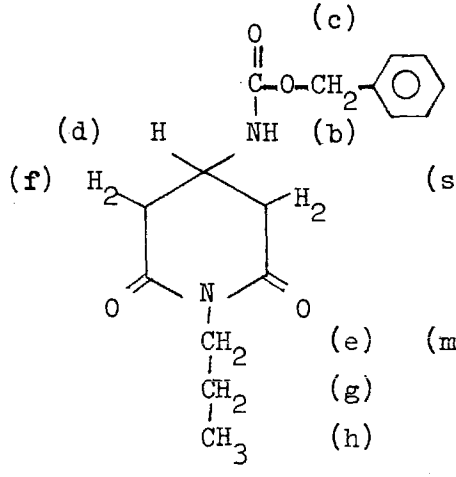


(acetone-d_6)

(a)	(b)	(c)
9.6	7.4	6.8
(broad, 1H)	(singlet, 5H)	(broad, 1H)

(d)	(e)	(f)	(g)
5.2	4.3	2.9	2.8
(singlet, 2H)	(multiplet, 1H)	(singlet, 2H)	(doublet, 2H)

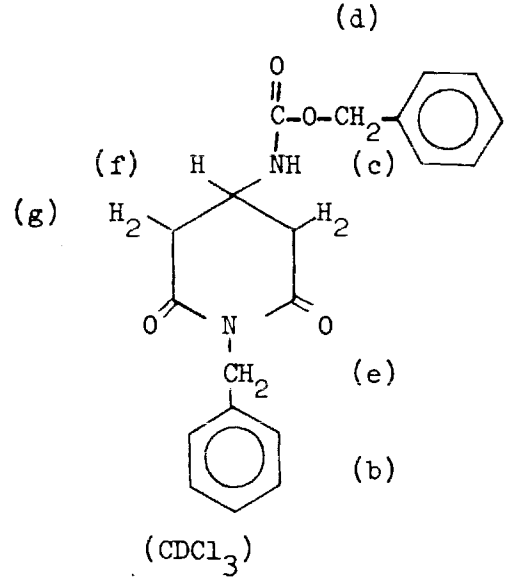
Table 4. (Continued).



(a)	(b)	(c)
7.3	5.5	5.0
(singlet, 5H)	(doublet, 1H)	(singlet, 2H)
(d)	(e)	(f)
4.1	3.7	2.8
(multiplet, 1H)	(triplet, 2H)	(triplet, 4H)
(g)	(h)	
1.5	0.8	
(multiplet, 2H)	(triplet, 3H)	

($CDCl_3$)

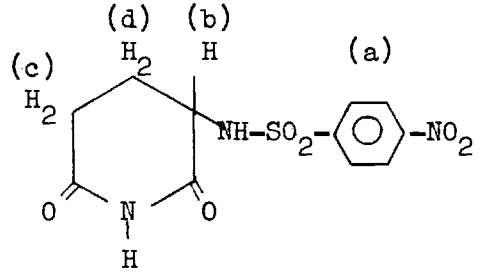
Table 4. (Continued).



(a)	(b)	(c)	(d)
7.3	7.2	5.2	5.1
(singlet, 5H)	(singlet, 5H)	(singlet, 1H)	(singlet, 2H)

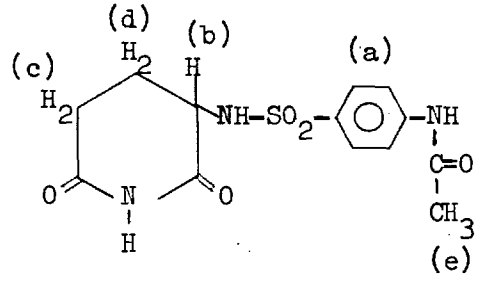
(e)	(f)	(g)
4.9	4.0	2.8
(singlet, 2H)	(broad, 1H)	(triplet, 4H)

Table 4. (Continued).



(pyridine-d_5)

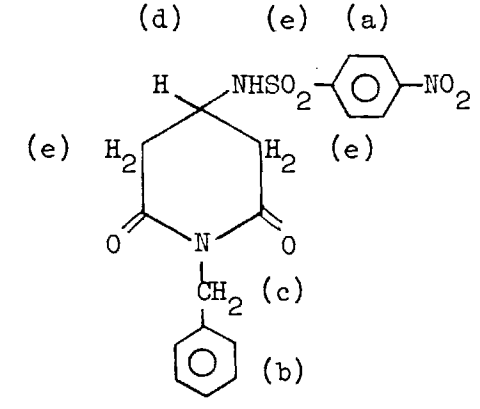
(a)	(b)	(c)	(d)
7.6	4.0	2.1	1.7
(singlet, 4H)	(multiplet, 1H)	(multiplet, 2H)	(multiplet, 2H)



(pyridine-d_5)

(a)	(b)	(c)	(d)	(e)
7.3	3.8	1.9	1.5	1.3
(doublet, 4H)	(multiplet, 1H)	(multiplet, 2H)	(multiplet, 2H)	(singlet, 3H)

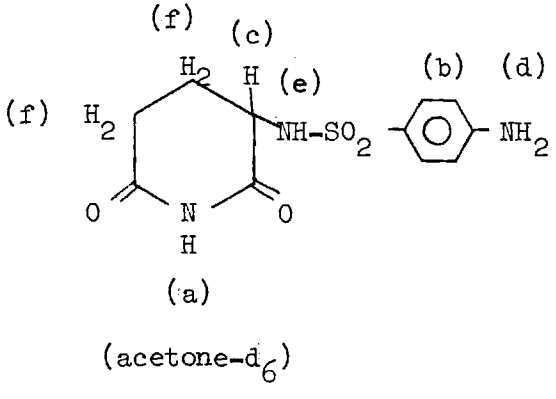
Table 4. (Continued).



(acetone-d_6)

(a)	(b)	(c)	(d)
8.8	7.3	4.9	4.1
(quartet, 4H)	(singlet, 4H)	(singlet, 2H)	(broad, 1H)

(e)
2.9
(multiplet, 5H)



(acetone-d_6)

(a)	(b)	(c)	(d)
9.0	7.5	5.5	4.8
(broad, 1H)	(quartet, 4H)	(broad, 1H)	(broad, 2H)

(e)	(f)
3.3	2.2
(multiplet, 1H)	(multiplet, 4H)

CHAPTER III

EXPERIMENTAL

All melting points are recorded in degrees Centigrade and are uncorrected. Melting points were determined in capillary tubes of 1.5-2.0 mm (OD) on a Mel-Temp melting point apparatus. To insure consistency the same thermometer was used for all melting point determinations. Elemental microanalyses were performed by Atlanta Micro-Laboratories, Atlanta, Georgia, unless otherwise noted. Infrared spectra were recorded using a Perkin-Elmer Model 700 spectrophotometer. Infrared spectra of solid samples were determined using potassium bromide pellets while spectra of liquids were determined employing liquid films on sodium chloride plates. Nuclear magnetic resonance spectra were obtained with a Varian Associates Model A-60D spectrometer. Mass spectral data was obtained using a Varian Associates Model M-66 mass spectrometer.

Ultra-violet spectra were recorded using a Cary Model 14 Recording Spectrophotometer. Spectral data are reported throughout the experimental section, and the appendix contains the complete spectra of a number of compounds whose preparations have been herein described.

Attempted Synthesis of 4-Chloroglutarimide

Synthesis of β-Chloroglutaric Acid

Acetonedicarboxylic Acid. The general method of Ingold and Nickolls (26) was used for the preparation of this compound. To 180 g. (0.84 mole) of crystalline citric acid monohydrate contained in a four liter beaker was slowly added 360 g. of fuming sulfuric acid (20 percent free SO_3). The sulfuric acid was added at a rate such that vigorous manual stirring could control the excessive foaming in the beaker as the reaction proceeded. The solution was thoroughly stirred for 15 minutes then was cooled to 10° in a dry-ice/acetone bath. To the stirred yellow liquid was added 100 g. of ice over a short period. After being stirred at 10° for an additional five minutes, a precipitate suddenly formed.

The product was filtered in a Buchner funnel using glass wool as the filtering medium. The white solid thus obtained was washed with several small portions of cold ethyl acetate and was sucked as dry as possible. After efforts to purify the acetonedicarboxylic acid gave poor yields, the crude product was used directly for the preparation of diethyl acetonedicarboxylate.

Diethyl Acetonedicarboxylate. The procedure followed for the esterification of acetone dicarboxylic acid was that of Adams and Chiles (2). To a solution of 550 ml. of absolute ethanol containing 125 g. of HCl was added the crude acetonedicarboxylic acid produced by the reaction of fuming sulfuric acid and 540 g. of citric acid monohydrate. The ethanol solution was heated to 40° and was stirred and shaken until

all of the solid had dissolved. After stirring the solution overnight at room temperature, it then was poured into 1100 ml. of iced water. The lower, organic layer was removed in a separatory funnel, and the aqueous layer was subsequently extracted with two 550 ml. portions of benzene. The extracts were combined and the resulting solution was washed with 300 ml. of 10 percent sodium carbonate solution, 300 ml. of dilute sulfuric acid, and two 300 ml. portions of water. The benzene was removed from the solution using a rotary evaporator. The product itself was purified by vacuum distillation, b. p. 130-137°/10 mm., lit. (2) b. p. 131-136°/10 mm. The pure ester weighed 127 g., representing a 25 percent yield based on the amount of citric acid used in the first step of the synthesis. The product yields obtained were less than those reported by Adams and Chiles, probably because lower yields of crude acetonedicarboxylic acid were obtained using the procedure of Ingold and Nickolls (25) than were obtained by Adams and Chiles (2) using a more time consuming preparation.

The IR spectrum showed absorptions at 1740 cm^{-1} (strong, carbonyl) and 1720 cm^{-1} (strong, carbonyl. The NMR spectrum as determined in carbon tetrachloride showed bands at 4.0δ(multiplet, 4H), 3.4δ (singlet, 4H), and 1.0δ (triplet, 6H). The mass spectrum showed the molecular ion at 202 amu.

Diethyl β-Hydroxyglutarate. In a 300 ml. pressure bottle was placed 20 g. (0.10 mole) of diethyl acetonedicarboxylate, 70 ml. of absolute ethanol, and 0.4 g. of platinum oxide. The bottle was placed on a Parr hydrogenation apparatus, and was treated with

hydrogen for three hours at an initial gauge pressure of 50 psi. When hydrogen uptake had ceased after a pressure drop of 8.3 psi, the bottle was removed from the machine. The catalyst was removed by filtration and the solvent was stripped on a rotary evaporator, leaving a colorless liquid. The crude product was purified by vacuum distillation, b. p. 154-155°/15 mm., lit. (12) b. p. 154-157°/11 mm. The pure diethyl β-hydroxyglutarate weighed 16.9 g. (85 percent yield).

An IR spectrum of the product contained absorptions at 1740 cm^{-1} (strong, carbonyl). The NMR spectrum gave absorptions at 4.0δ (multiplet, 5H), 3.6δ (singlet, 1H), 2.4δ (doublet, 4H), and 1.1δ (triplet, 6H). The mass spectrum did not reveal a molecular ion, but contained a peak corresponding to m-45, corresponding to loss of an ethyl group.

Attempts to prepare diethyl β-hydroxyglutarate from α-dichlorohydrin using the method of Dreifuss and Ingold (12) proved largely unsuccessful. Yields of the desired ester were very poor, as was the purity of the product. Due to the success of the above procedure, very little attention was focused on this second method of preparing the hydroxy ester.

Diethyl β-Chloroglutarate. The method utilized for this preparation was adapted from that of Grundeman and Paul (21). In a 250 ml. three-necked flask fitted with a dropping funnel was placed 40 ml. of carbon tetrachloride and 40 g. (0.19 mole) of phosphorous pentachloride. The magnetically stirred flask was immersed in an ice bath and a solution of 35 g. (0.17 mole) of diethyl β-hydroxyglutarate

in 50 ml. of carbon tetrachloride was added in a dropwise fashion over a 45 minute period. The solution was stirred at 0° for another 30 minutes, then 100 ml. of iced water was added and the solution was stirred vigorously for 1.5 hours. The organic layer was isolated in a separatory funnel, and the solvent was removed on a rotary evaporator. The product was distilled under vacuum, b. p. 104-108°/ 1.3 mm., lit. (46) b. p. 140°/11 mm. The weight of distilled product was 25 g., representing a 65 percent yield.

The IR spectrum of the purified product contained IR absorptions at 1740 cm^{-1} (strong, carbonyl). The NMR spectrum showed peaks at 4.5δ (multiplet, 1H), 4.1δ (quartet, 4H), 2.7δ (doublet, 4H), and 1.2δ (triplet, 6H). The mass spectrum did not show a molecular ion, but showed a peak at m-45 corresponding to loss of an ethyl group.

β-Chloroglutaric Acid. To 40 ml. of concentrated hydrochloric acid was added 5 g. (0.022 mole) of diethyl β-chloroglutarate. The solution was stirred magnetically for four days at room temperature. The solution was extracted with three 100 ml. portions of diethyl ether. The ether extracts were combined, washed with 50 ml. of water, and dried over magnesium sulfate. The ether was removed on a rotovap to give 3.0 g. of white solid. The crude product was recrystallized from benzene/ethyl acetate to give 1.5 g. (40 percent yield) of β-chloroglutaric acid, m. p. 128-129°, lit (46) m. p. 128-130°.

The IR spectrum of the product had strong carbonyl absorptions

at 1710 cm^{-1}. The NMR spectrum gave absorption bands at 7.3δ (broad, 2H), 4.0δ (triplet, 1H), and 2.3δ (multiplet, 4H). The mass spectrum did not show a molecular ion, but did have a peak at m/e 149 due to loss of H_2O from the parent ion.

Attempted Dehydration of Ammonium β-Chloroglutarate

In a 100 ml. round bottomed flask was placed 4.0 g. (0.024 mole) of β-chloroglutaric acid and 40 ml. of concentrated ammonium hydroxide solution. The resulting solution was stirred for several minutes, then was placed on a rotary evaporator. The excess ammonia was removed at room temperature, then the water was stripped off at 50°, leaving a white solid in the flask. An IR of the product was considerably different from the starting material. As expected the C=O stretching vibrations were broadened and shifted to lower wavelength, but the C-Cl stretching absorptions at 700 cm^{-1} had disappeared. It would appear that the material had been dehydrohalogenated during the conversion to the ammonium salt of the carboxylic acid. An effort was made to cyclize the hoped for ammonium β-chloroglutarate by heating, a common literature (33,6) preparation of glutarimides. The solid produced above was placed in a 50 ml. Erlenmeyer flask, and the flask was immersed in an oil bath maintained at 180°, during which time ammonia was evolved. After 45 minutes the flask was removed from the bath and was cooled. The black residue in the flask was treated with 30 ml. of boiling ethanol which dissolved about two-thirds of the material present. The ethanol solution was chilled several days, but no product crystallized. The reaction was

terminated at this point since it was felt that the starting material had been badly degraded while preparing its ammonium salt and during the heating in the oil bath. The reaction was repeated twice with similar results.

Attempted Cyclization of β-Chloroglutaric Acid in Formamide

In a procedure adapted from that of Sugasawa and Shigehara (42), four grams of β-chloroglutaric acid were dissolved in 10 ml. of formamide. The solution was heated to 170° and was maintained at that temperature for four hours. The solution was then cooled and 30 ml. of a 5 percent sodium carbonate solution was added. After thoroughly chilling of this mixture for several days, since no material precipitated from the solution the mixture was extracted with 80 ml. of chloroform. Following removal of the chloroform only a small amount of formamide remained and no material whose IR spectrum contained carbonyl absorptions attributable to an imide was found. The reaction mixture was finally abandoned in favor of other cyclization methods.

Attempted Cyclization of β-Chloroglutaric Acid with Sulfamide

In another attempt to prepare 4-chloroglutarimide, the procedure of Kirsanov and Zolatov (28) was employed. To 15 ml. of dry pyridine were added 4 g. (0.024 mole) of β-chloroglutaric acid and 2.75 g. (0.029 mole) of sulfamide. While being refluxed for three hours, the solution was stirred magnetically.

When the solution was cooled, an insoluble gum was noted in the bottom of the reaction flask. The solution was added to 10 ml. of 10

percent sodium carbonate solution and the resulting solution was evaporated to dryness on a rotary evaporator. The dry residue was extracted with two 25 ml. portions of chloroform. After removal of the chloroform on a rotary evaporator, no observable residue remained. Similar results were obtained when the reaction was repeated and the reaction scheme was finally terminated when no neutral product could be obtained. No attempt was made to determine the nature of the material which was insoluble in chloroform.

Synthesis and Attempted Reduction of 4-Iminoglutarimide

Preparation of 4-Iminoglutarimide

Ethyl β-Iminoglutaramate. The procedure described by Stokes and Von Pechman (41) was followed for the preparation of this compound. In a 200 ml. pressure bottle was placed 27.5 g. (0.14 mole) of diethyl acetonedicarboxylate, and 25 ml. of water saturated at 0° with ammonia was carefully added to avoid mixing of the two layers. The bottle was stoppered and clamped shut, then was shaken until a homogeneous solution resulted. The bottle was allowed to stand for 36 hours, during which time the contents solidified. The bottle was unsealed and the contents were filtered, sucked to dryness, and twice recrystallized from water to give 13 g. (65 percent yield) of white crystals, m. p. 83-85°, lit. (41) m. p. 86°.

The IR spectrum of the product showed strong carbonyl absorptions at 1650, 1620 and 1560 cm^{-1}. The mass spectrum gave a molecular ion at m/e 172.

4-Iminoglutarimide. This compound was prepared by a procedure reported by Stokes and Von Pechman (41). To a solution of 6.0 g. (0.057 mole) sodium carbonate in 22 ml. of water was added 6.0 g. (0.035 mole) of β-imidoglutamic ethyl ester. The solution was heated to reflux for 10 minutes, during which time ammonia gas was evolved from the reaction solution. After refluxing the solution was allowed to cool to room temperature and then was made acidic with acetic acid which caused formation of a precipitate. The solution was cooled overnight then filtered to give 1.6 g. (37 percent yield) of light pink crystals, m. p. 305°, dec., lit. (41) m. p. 300° dec. The product was found to be quite insoluble in nearly all common organic solvents.

The IR spectrum of the material contained absorptions at 1700, 1620 and 1580 cm^{-1} (strong, carbonyl). No NMR spectrum was obtained due to the lack of a suitable solvent.

Attempted Hydrogenation of 4-Iminoglutarimide

To 20 ml. of dry dimethylsulfoxide was added 0.75 g. (0.006 mole) of 4-iminoglutarimide. When the solid had completely dissolved one ml. of acetic acid and 0.2 g. of 10 percent palladium/carbon catalyst were added, and the solution was treated with hydrogen at an initial gauge pressure of 50 psi on a Parr hydrogenation apparatus. After four hours the solution was removed from the Parr Shaker, although no pressure drop had been observed. The catalyst was removed by filtration, leaving a black solution which had a nauseating odor. No precipitate formed when the solution was acidified with five ml.

of ethanolic hydrogen chloride and the resulting solution was poured into 100 ml. of diethyl ether.

The ether was removed and an effort was made to remove the dimethylsulfoxide from the solution using a rotary evaporator. Unfortunately, the bath temperature was too high and the solution was badly decomposed. No other attempts were made to achieve the desired reduction. The lack of solubility of the glutarimide derivative in common hydrogenation solvents was a considerable deterrent to the success of such a reaction.

Synthesis of β-Glutamic Acid

Attempted Preparation of β-Glutamic Acid from Diethyl Acetonedicarboxylate Tosylhydrazone

Diethyl Acetonedicarboxylate Tosylhydrazone. In 200 ml. of absolute ethanol were dissolved 6.20 g. (0.033 mole) of diethyl acetonedicarboxylate and 6.70 g. (0.033 mole) of tosylhydrazine. The solution was stirred at room temperature overnight, then was concentrated to a volume of 50 ml. using a rotary evaporator. A precipitate formed after the solution was thoroughly chilled. Filtration yielded 11.0 g. (90 percent yield) of white crystals, m. p. 88-89°. A 1.8 g. portion of the product was recrystallized from 50 ml. of aqueous ethanol to give 1.4 g. (80 percent recovery) of product, m. p. 90-91°. An IR spectrum showed both sulfonamide S=O stretching absorptions at 1100 and 1350 cm^{-1} and carbonyl C=O stretching absorptions at 1740 cm^{-1}. The NMR spectrum gave absorption bands at

6.9δ (multiplet, 4H), 3.4δ (multiplet, 4H), 2.9δ (singlet, 2H), 2.7δ (singlet, 2H), 2.1δ (singlet, 1H), 1.75δ (singlet, 3H), and 0.5δ (triplet, 6H).

$C_{16}H_{22}N_2O_6S$	Calculated:	C, 51.89; H, 5.59; N, 7.57; S, 8.65.
	Found:*	C, 51.99; H, 5.96; N, 7.43; S, 8.50.

Attempted Hydrogenolysis of Diethyl Acetonedicarboxylate Tosylhydrozone. To 75 ml. of absolute ethanol contained in a 300 ml. pressure bottle was added 2.12 g. (0.006 mole) of diethyl acetonedicarboxylate tosylhydrazone and 0.2 g. of platinum oxide. The solution was shaken with hydrogen for two days at a gauge pressure of 50 psi on a Parr hydrogenation apparatus. No pressure drop other than that due to normal leakage was observed during the reaction period. The bottle and its contents were removed from the apparatus and the catalyst removed by filtration. The filtered solution was concentrated to a volume of 15 ml. on a rotary evaporator and was chilled for two hours. The solution was then filtered to give 1.5 g. of white solid which was identified as starting material by mixed melting point and comparison of an IR spectrum with that of a known sample. After removal of the crystallized starting material, the filtrate was added to 100 ml. of diethyl ether and hydrogen chloride

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* Performed by Galbraith Laboratories, Knoxville, Tennessee.

was bubbled through the solution for 20 minutes. No precipitate or turbidity appeared upon acidification of the solution. The solvent was removed on a rotary evaporator, leaving 0.4 g. of white solid which was shown to be the starting ester by comparison of an IR spectrum to that of a known sample.

Similar results were obtained when 5 percent palladium on carbon was used as the catalyst and when acetic acid was used as the solvent. The attempted hydrogenolysis was abandoned when other pathways led to the production of β-glutamic acid in good yields.

Preparation of β-Glutamic Acid from Diethyl 3-Iminoglutarate

Diethyl β-Iminoglutarate. The general method of Emery (15) was used for this preparation. In a 300 ml. pressure bottle was placed 30 ml. (34 g., 0.16 mole) of diethyl acetonedicarboxylate. A solution of 60 ml. of ethanol which was saturated at 0° with ammonia was added and the bottle was stoppered, clamped securely, and shaken until a homogeneous solution formed. The resulting solution was allowed to stand at room temperature for two days, during which time a green color developed. The bottle was opened and the ethanol was removed on a rotavap. The residual blue-green oil was purified by vacuum distillation to give 10.3 g. (30 percent yield) of colorless liquid, b. p. 145°/1 mm. lit. (15) b. p. 158°/11 mm. In later preparations, the crude product was reacted directly in subsequent reactions without further purification. The mass spectrum of the compound showed a molecular ion at m/e 201.

Diethyl β-Aminoglutarate. The method employed in this reaction is similar to the method used by Herbst and Shemin (24) for the reduction of α-acetamidocinnamic acid. In a 300 ml. pressure bottle was placed 40 ml. of acetic acid and the unpurified product prepared by the action of an ethanolic ammonia solution on 22 g. (0.11 mole) of diethyl acetonedicarboxylate. After the addition of 0.2 g. of platinum oxide catalyst, the solution was treated with hydrogen at an initial gauge pressure of 50 psi for 16 hours. The catalyst was removed by filtration and the solvent was stripped on a rotary evaporator, leaving a green oil. An IR spectrum of the crude product showed N-H stretching vibrations at 3500 cm^{-1} and ester carbonyl C=O absorption at 1740 cm^{-1}. The product was hydrolyzed with no further purification to β-glutamic acid.

β-Glutamic Acid. Diethyl β-glutamate was hydrolyzed using a procedure similar to that of Friedman and Kosower (17). To the crude product from the reaction described above was added 350 ml. of concentrated hydrochloric acid. The solution was stirred for two days at room temperature, then was stripped to dryness on a rotary evaporator. The resultant brown residue was dissolved in 100 ml. of water and the pH was adjusted to 3.6, whereupon a precipitate began to form. The solution was thoroughly chilled, then was filtered to give 5.0 g. of light grey powder, m. p. 290° dec., lit. (17) m. p. 295° dec. The 5.0 g. of product represents a 31 percent yield, based upon the amount of diethyl acetonedicarboxylate with which the synthesis was begun. Overall yields of other preparations were as high as 50 percent.

Synthesis of Substituted Glutamine Derivatives

Preparation of Carbobenzoxyglutamine

Following the procedure of Bruckner, Kovacs, and Kovacs, (9) 30 g. (0.20 mole) of L-(+)-glutamine was dissolved in 540 ml. of a 3.3 percent sodium bicarbonate solution (0.21 mole). When all of the solid had dissolved, an additional 60 g. (0.71 mole) of sodium bicarbonate was added. The magnetically stirred solution was cooled in an ice bath and 73 g. (0.43 mole) of carbobenzoxy chloride was added from a dropping funnel over a period of 20 minutes. The stirred solution was kept immersed in the ice bath for a total of one hour, then the bath was removed and the solution was stirred at room temperature for an additional three hours. Excess carbobenzoxy chloride was removed by extracting the reaction solution with two 200 ml. portions of ethyl acetate. The aqueous solution was then acidified with hydrochloric acid and was thoroughly chilled. Filtration of the solution gave 40 g. of crude product, which was recrystallized from an ethyl acetate-hexane solution to give 32 g. (56 percent yield) of white crystals, m. p. 132-133°, lit. (9) m. p. 135°. An IR spectrum of the product contained carbonyl absorptions at 1730 cm^{-1} (medium), 1680 cm^{-1} (strong), and 1660 cm^{-1} (strong).

Preparation of Substituted Carbobenzoxyglutamines

Carbobenzoxyglutamic Acid. The method of Bergman and Zervas (5) was employed for this preparation. To 100 ml. of water contained in a 250 ml. Erlenmeyer flask were added 8.8 g. (0.06 mole) of D-(+)-glutamic acid and 7.4 g. of magnesium oxide. The solution was stirred

magnetically for one hour at room temperature. After addition of 50 ml. of ether, the solution was cooled in an ice bath and 20.4 g. (0.12 mole) of carbobenzoxy chloride was added dropwise over a 30 minute period with vigorous stirring. The ice bath was removed and the solution was stirred at room temperature for three and one-half hours. Excess carbobenzoxy chloride was extracted with ethyl acetate and the solution was acidified with concentrated hydrochloric acid. After acidification the solution was extracted with 100 ml. of ethyl acetate which then was dried over magnesium sulfate. The ethyl acetate was removed on a rotary evaporator leaving an oil in the evaporating flask. The oil was crystallized from a 1:2 mixture of ethyl acetate-hexane to give a white solid which was recrystallized from the same solvent system to give 14.8 g. (88 percent yield) of white crystals, m. p. 117-118°, lit. (5) m. p. 120°.

Carbobenzoxyglutamic Anhydride. This compound was prepared by the procedure used by Khedouri and Wellner (27). To 10 g. (0.036 mole) of carbobenzoxyglutamic acid contained in a flask fitted with a reflux condenser was added 120 ml. of acetic anhydride. The flask and its contents were heated on a steam bath for 30 minutes, then were cooled to 50°. Excess acetic anhydride was removed on a rotary evaporator leaving a colorless oil as a residue. The crude carbobenzoxyglutamic anhydride thus obtained was used for subsequent reactions without any further attempts at purification.

N^5-Benzyl Carbobenzoxyglutamine. The original synthesis of this material was taken from the method used by Edelson, Skinner and Shive (14) for the preparation of N^5-substituted carbobenzoxyglutamines, although later preparations utilized a different solvent. The carbobenzoxyglutamic anhydride prepared from 10 g. (0.036 mole) of carbobenzoxyglutamic acid was dissolved in 120 ml. of a 1:1 mixture of benzene and ethanol, and 4 ml. (4.0 g., 0.037 mole) of benzyl amine was immediately added. The solution was stirred overnight at room temperature during which time a precipitate formed. After the solvent was removed on a rotovap the resulting solid was recrystallized from ethanol-hexane to give 5.7 g. of white crystals, m. p. 152-154°. The product was recrystallized a second time from the same solvent system, giving 4.5 g. (33 percent yield) of crystals, m. p. 167-168°, lit. (14) m. p. 147°.

The IR spectrum showed significant bands at 3300 cm^{-1} (weak), N-H stretch; 1720 cm^{-1} (strong), 1650 cm^{-1} (shoulder),and 1630 cm^{-1} (strong),C=O stretch; and 1540 cm^{-1} (strong), N-H bend. No molecular ion was observed in the mass spectrum.

Since the melting point of the product differed so greatly from the literature value, an analysis was obtained.

$C_{20}H_{22}N_2O_5$	Calculated:	C, 64.84; H, 5.99; N, 7.57.
	Found:	C, 64.64; H, 6.08; N, 7.59.

No reason is known for the difference in the melting point of the product and its reported melting point. Since the literature preparation used only one recrystallization, it is possible the reported product was not completely pure.

In later preparations of this product, chloroform was used as the reaction solvent. No differences were observed in the yields obtained or in the melting point of the product produced.

N^5-Benzyl Carbobenzoxyglutamine Methyl Ester. In 100 ml. of warm methanol was dissolved 5.5 g. (0.015 mole) of N-benzyl carbobenzoxyglutamine. The solution was cooled to room temperature and was treated with a solution of 2g. (0.05 mole) of diazomethane dissolved in 200 ml. of diethyl ether.

After the solution was let to stand for two hours, the solvent was removed on a rotary evaporator leaving a white solid. The solid was dissolved in ethyl acetate and the resulting solution was extracted with 10 percent sodium hydroxide solution. After the organic layer was dried, the solvent was removed on a rotary evaporator. The 5.6 g. of resultant product (98 percent yield) m. p. 114-116°, was recrystallized from an ethanol-hexane solution to give 4.5 g. of white solid, m. p. 114-115°.

The IR spectrum showed absorptions at 3300 cm^{-1} (strong), N-H stretch; 1730 cm^{-1} (strong), 1690 cm^{-1} (strong), and 1650 cm^{-1} (strong), C=O stretch; and 1540 cm^{-1} (strong), N-H bend. The NMR spectrum contained absorption bands at 7.0δ (singlet, 5H); 6.9δ (singlet, 5H), 6.0δ (broad, 1H), 4.8δ (singlet, 2H), 4.0δ (doublet, 2H),

3.3δ (singlet, 3H), 2.5δ (singlet, 1H), and 2.0δ (multiplet, 4H). A small molecular ion at m/e 384 appeared in the mass spectrum of the product.

$C_{21}H_{24}N_2O_5$	Calculated:	C, 65.63; H, 6.25, N, 7.29.
	Found:	C, 65.54; H, 6.32; N, 7.32.

N^5-Phenyl Carbobenzoxyglutamine. The procedure used above for the preparation of N-benzyl carbobenzoxyglutamine was also used for other derivatives. Again, no differences in the yields or melting points of products were observed when the solvent was changed from ethanol-benzene to chloroform. A typical reaction involved conversion of 10 g. (0.036 mole) of carbobenzoxyglutamic acid to the corresponding anhydride, followed by reaction of the anhydride with 3.6 g. (0.037 mole) of aniline in 120 ml. of 1:1 ethanol-benzene solution. After working up the reaction, 4.2 g. (33 percent yield) of white solid, m. p. 193-194°, lit. (14) m. p. 157°, was obtained. An analysis was not performed, but analyses of derivatives prepared from this product gave the required results.

The IR spectrum of the product contained absorptions at 3300 cm^{-1} (strong), N-H stretch; 1720 cm^{-1} (strong), 1680 cm^{-1} (strong), and 1640 cm^{-1} (strong), carbonyl C=O stretch; and 1530 cm^{-1} (strong), N-H bend. A mass spectrum contained a peak corresponding to a molecular ion at m/e 356.

Preparation of N^5-Substituted Glutamines

N-Benzyl Glutamine. A modified procedure similar to that of Edelson, Skinner and Shive (14) was used for the hydrogenolysis of N-benzyl carbobenzoxyglutamine. In a 300 ml. pressure bottle was placed 3 g. (8.0 mmole) of N-benzyl carbobenzoxyglutamine, 40 ml. of ethanol, and 25 ml. of water. The solution was heated until the solid had completely dissolved, then was cooled to room temperature, and 0.3 g. of 10 percent palladium on carbon was added. The solution was treated with hydrogen at 30 psi initial gauge pressure on a Parr apparatus for a period of five hours. The catalyst was removed by filtration and the solvent was taken off on a rotary evaporator, leaving a white solid. The solid was recrystallized from ethanol containing a small amount of water to give 1.12 g. (59 percent yield) of white crystals, m. p. 147-148°, lit. (14) m. p. 225-226°.

The IR spectrum showed absorptions at 1670 cm^{-1} (strong), C=O stretch, and 1560 cm^{-1} (strong), carboxylate anion stretch. No NMR spectrum was determined. The mass spectrum of the product did not contain a molecular ion. An analysis was obtained on the product, since the observed melting point did not correspond to the recorded melting point.

$C_{12}H_{16}N_2O_3$ Calculated: C. 61.00; H, 6.83;
N, 11.86.
Found: C, 60.75; H, 6.87;
N, 11.85.

N^5-Phenyl Glutamine. The procedure described above was also used for the hydrogenolysis of N-phenyl carbobenzoxyglutamine. In 200 ml. of ethanol was dissolved 6.0 g. (0.017 mole) of N-phenyl carbobenzoxyglutamine. To the solution was added 25 ml. of water and 0.3 g. of 10 percent palladium on carbon. The solution was treated overnight with hydrogen at a gauge pressure of 50 psi, then the catalyst was filtered and the solvent was removed on a rotovap, leaving a white solid. The solid was recrystallized from a water-ethanol solution to give 2.2 g. (60 percent yield) of white solid, m. p. 175-176°, lit. (14) m. p. 197-199°.

Important absorptions in the IR spectrum were observed at 1690 cm^{-1} (strong), C=O stretch; and 1550 cm^{-1} (strong), carboxylate anion. The NMR spectrum obtained in D_2O showed absorptions at 7.5δ (singlet, 5H), 4.3δ (multiplet, 1H), and 2.4δ (multiplet, 4H). The mass spectrum contained a small molecular ion at m/e 222.

An analysis gave the indicated results.

$C_{11}H_{14}N_2O_3$	Calculated:	C, 59.46; H, 6.31; N, 12.61.
	Found:	C, 59.52; H, 6.40; N, 12.57.

Determination of α-Amino Acid Content of N-Substituted Glutamines

The α-amino acid content of the N-phenyl glutamine and N-benzyl glutamine prepared by the above procedures was determined by the method of Spies (40). This procedure is based on the fact that α-

amino acids form complexes with copper ions, whereas γ- and δ-amino acids do not. Solutions necessary for the determination consist of 8.52 g. of cupric chloride dihydrate in one liter of water, a sodium borate buffer composed of 10.1 g. of anhydrous sodium tetraborate and 60 g. of sodium chloride in one liter of water, and an amino acid solution containing 50 to 500 micromoles of acid per liter.

The general procedure for the preparation and determination of the copper complexes was as follows. In a 15 ml. centrifuge tube was placed 5.0 ml. of buffer solution and 5.0 ml. of the amino acid solution. After mixing, 0.10 ml. of the cupric chloride solution was added, and the tubes were stoppered and shaken for 15 seconds. After standing undisturbed for exactly 10 minutes, the solutions were centrifuged for five minutes. The supernatant liquid was transferred to a UV cuvette and the percent transmittance was measured at 230 millimicrons, using as a reference sample an identically treated sample to which no copper solution was added. The exact volume of the copper solution dispensed and the length of time the tubes were allowed to stand were both found to be critical to the success of the method.

A series of alanine solutions ranging in concentration from 0-500 micromolar was prepared as a reference. Using the above procedure, a plot of the log of the percent transmittance versus the concentration of the solution was prepared (Figure 28). This procedure gave a straight line plot in the concentration range employed. When this reference plot was established, it was used as a standard to determine the α-amino acid content of other solutions.

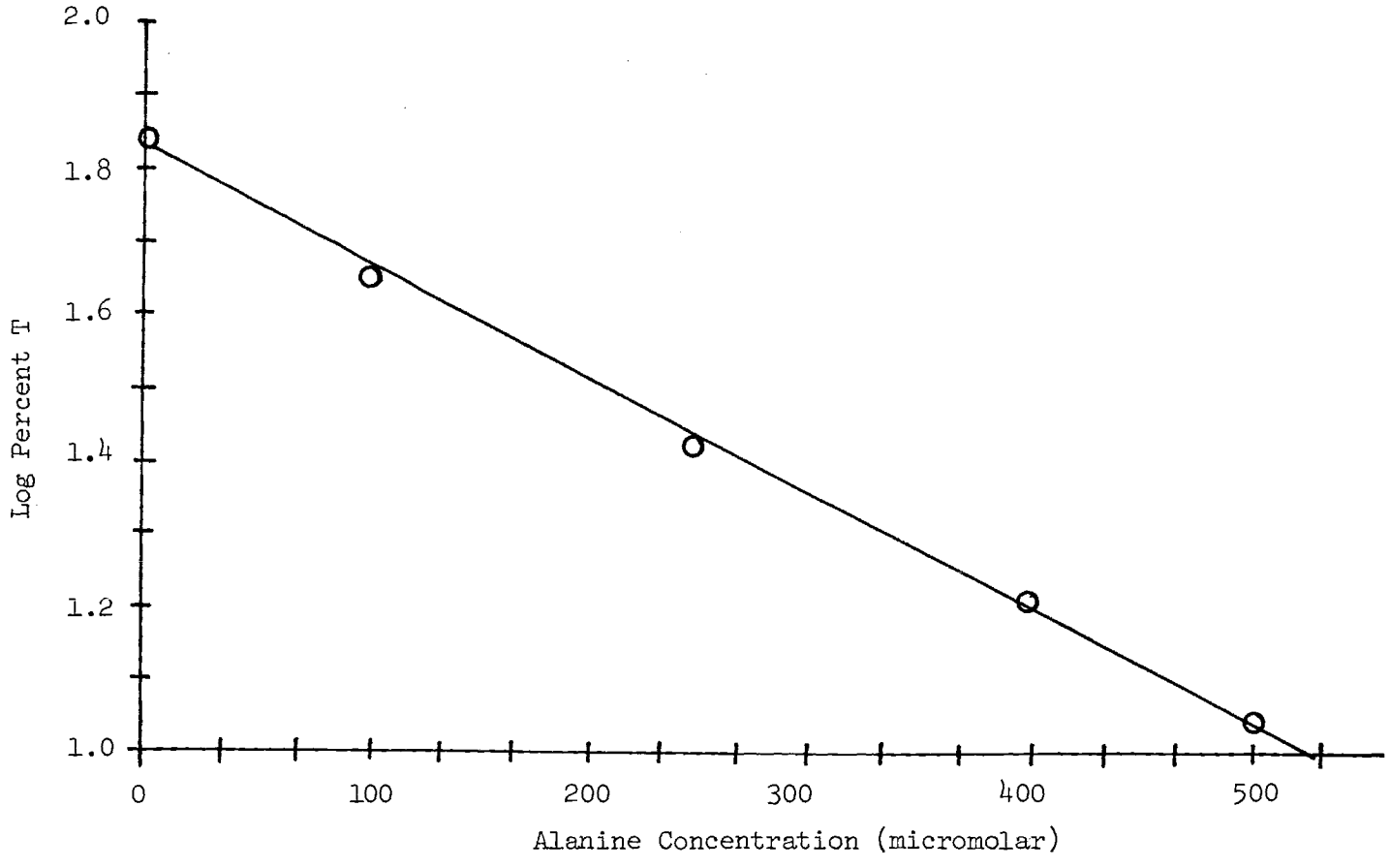

Figure 28. Plot of Alanine Concentration Versus Log (Percent Transmittance)

alanine concentration (micromoles per liter)	% T	Log % T
0	68.0	1.83
100	46.0	1.66
250	27.0	1.43
400	16.7	1.22
500	11.0	1.04

The unknown acid was subjected to the previously described procedure, and the transmittance of the resulting solution was determined. This transmittance was used to determine the concentration of the alanine solution which would give the same percent transmittance. The α-amino acid percentage was then determined from the formula below.

$$\alpha\text{-amino acid content} = \frac{\text{corresponding alanine concentration}}{\text{amino acid concentration}} \times 100\ \%$$

This test was applied to several known amino acids as a check before determining acids of unknown content. Glutamine and glutamic acid gave results which corresponded to 100 percent α-amino acid content. An α-amino acid content of zero percent was determined for 4-amino-butyric acid, 6-aminocaproric acid, and 4-aminobenzoric acid.

After preparing the reference plot and testing the known amino acids as described above, the N-Phenyl glutamine and N-benzyl glutamine reported in this work were subjected to the procedure. The results indicated that the N-phenyl glutamine contains no α-amino acid and is therefore more likely N-phenyl isoglutamine, and that the

N-benzyl glutamine contains an α-amino acid content of 70 percent.

Amino Acid	Concentration (micromoles/liter)	% T	Log % T
Glutamic Acid	250	26.2	1.42
p-Aminobenzoic Acid	250	73.0	1.86
6-Aminocaproic Acid	297	78.8	1.62
4-Aminobutyric Acid	217	65.0	1.45
N-Phenyl Glutamine	216	67.0	1.47
N-Benzyl Glutamine	246	37.0	1.57
N-Benzyl Glutamine	263	45.3	1.66

Synthesis of β-Glutamine Derivatives

Preparation of Carbobenzoxy-β-glutamic Acid

The general procedure of Bergman and Zervas (5) was followed for the preparation of this product. To 180 ml. of water in a 250 ml. Erlenmeyer flask were added 14.7 g. (0.10 mole) of β-glutamic acid and 12.0 g. (0.30 mole) of magnesium oxide. The solution was stirred at room temperature for 30 minutes, then the flask and its contents were cooled in an ice bath. The solution was covered with 50 ml. of diethyl ether and 34 g. (0.20 mole) of carbobenzoxy chloride was added during a period of 15 minutes. The ice bath was removed after 30 minutes and the solution was allowed to warm to room temperature and stir an additional seven hours. The solution was acidified and was extracted with two 200 ml. portions of ethyl acetate. The extracts were combined and dried over magnesium sulfate, and the ethyl acetate

was removed on a rotary evaporator. The resulting tan solid was recrystallized from ethyl acetate-hexane to give 21.0 g. (75 percent yield) of light tan solid, m. p. 161-162°, lit. (27) m. p. 163-165°.

The IR spectrum contained strong carbonyl absorptions at 1710 cm^{-1} (shoulder) and 1680 cm^{-1}. The NMR spectrum in acetone-d_6 showed bands at 7.4δ (singlet, 5H), 5.1δ (singlet, 2H), 4.4δ (triplet, 1H), and 2.7δ (doublet, 4H). The mass spectrum did not contain a molecular ion, but did contain a small peak at m/e 263 corresponding to the loss of a water molecule from the parent compound.

Preparation of Carbobenzoxy-β-glutamine

The method of Khedouri and Wellner (27), previously reported for the synthesis of carbobenzoxy-β-glutamine, was used with minor changes. In a 250 ml. round-bottomed flask were placed 10 g. (0.036 mole) of carbobenzoxy-β-glutamic acid and 120 ml. of acetic anhydride. The solution was stirred overnight at room temperature, then the acetic anhydride was removed on a rotary evaporator. The resulting oil was taken up in 200 ml. of chloroform and ammonia was bubbled into the resultant solution for 20 minutes at room temperature. The solution was cooled and the white precipitate which had formed was filtered. The solid thus obtained was dissolved in 150 ml. of water and the solution was acidified with hydrochloric acid, giving an immediate precipitate. The crude product was isolated by filtration and was recrystallized from water to give 8.3 g. (83 percent yield) of white crystals, m. p. 177-178°, lit. (27) m. p. 185°.

Important IR absorptions were observed at 1700 cm^{-1} (shoulder),

1680 cm^{-1} (strong), and 1650 cm^{-1} (strong), C=O stretch; and at 1530 cm^{-1} (strong), N-H bend. A molecular ion at m/e 280 was observed in the mass spectrum.

Preparation of N^5-Substituted Carbobenzoxy-β-glutamine Derivatives

N^5-Benzyl Carbobenzoxy-β-glutamine. The procedure previously described for the preparation of substituted glutamine derivatives was employed. Carbobenzoxy-β-glutamic anhydride, prepared by the reaction of 10.0 g. (0.036 mole) of carbobenzoxy-β-glutamic acid and excess acetic anhydride, was dissolved in 200 ml. of chloroform and 4.0 g.(0.037 mole) of benzyl amine was added to the stirred solution. A white precipitate formed soon after the addition of the benzyl amine. The solution was stirred overnight at room temperature, then was filtered to give 12 g. of white solid, m. p. 161-163°. The solid was recrystallized from ethanol-hexane to give 10.0 g. (75 percent yield) of white crystals, m. p. 148-149°. If the recrystallized product was melted, cooled, and remelted, the melting point increased to 162-163°.

The IR spectrum showed absorptions at 3350 cm^{-1} (strong), N-H stretch; 1700 cm^{-1} (shoulder), 1680 cm^{-1} (strong), and 1620 cm^{-1} (strong), C=O stretch; and at 1520 cm^{-1} (strong), N-H bend. Absorptions in the NMR spectrum obtained in acetone-d_6 were found at 7.4δ (singlet, 5H), 7.3δ (singlet, 5H), 6.5δ (broad, 1H), 5.1δ (singlet, 2H), 4.4δ (multiplet, 3H), and 2.7δ (multiplet, 4H). No molecular ion was observed in the mass spectrum, but a peak at m-18 was observed.

$C_{20}H_{22}N_2O_5$ Calculated: C, 64.86; H, 5.95;
N, 7.57.
Found: C. 64.66; H, 6.04;
N, 7.65.

N^5-Propyl Carbobenzoxy-β-glutamine. The carbobenzoxy-β-glutamic anhydride prepared by the action of acetic anhydride on 10 g. (0.036 mole) of β-glutamic acid was dissolved in 200 ml. of chloroform and 3.0 g. (0.037 mole) of n-propyl amine was added. After the solution had been stirred for 10 minutes, a precipitate began to form. The solution was stirred overnight at room temperature, then was filtered to give 8.5 g. of white solid, m. p. 176-178°. Recrystallization from ethanol-hexane gave 8.4 g. (72 percent yield) of product, m. p. 178-179°.

The IR spectrum contained absorptions at 1700 cm^{-1}, 1685 cm^{-1}, and 1610 cm^{-1}, (strong), C=O stretch, and 1520 cm^{-1} (strong), N-H bend. The NMR spectrum in pyridine-d_5 gave absorptions at 12.4δ (singlet, 1H), 7.4δ (multiplet, 5H), 5.3δ (singlet, 2H), 5.0δ (multiplet, 1H), 3.2δ (multiplet, 6H), 1.5δ (multiplet, 2H), and 0.9δ (triplet, 3H). The mass spectrum did not show a molecular ion.

$C_{10}H_{22}N_2O_5$ Calculated: C, 59.63; H, 6.83;
N, 8.70.
Found: C, 59.63; H, 6.85;
N, 8.74.

N^5-Propyl Carbobenzoxy-β-glutamine, Methyl Ester. To a solution of 5.0 g. (0.016 mole) of N-propyl carbobenzoxy-β-glutamine in 100 ml. of methanol was added an excess of diazomethane in 200 ml. of diethyl ether. The yellow diazomethane color disappeared quite rapidly upon standing. After the solution was allowed to stand for several hours the solvent was removed on a rotary evaporator leaving a white solid. The solid was dissolved in 150 ml. of ethyl acetate and the resulting solution was extracted with two 100 ml. portions of 5 percent socium bicarbonate solution and one 100 ml. portion of water. After being dried over magnesium sulfate, the ethyl acetate was removed on a rotary evaporator leaving 5.0 g. (95 percent yield) of white solid, m. p. 125-126°. A small sample was recrystallized from ethanol-hexane to give a white solid, m. p. 125-126°.

An IR spectrum showed absorption bands at 1730 cm^{-1} (strong), 1680 cm^{-1} (strong), and 1260 cm^{-1} (strong), C=O stretch; and 1520 cm^{-1} (strong), N-H bend. The NMR spectrum obtained in deuterochloroform contained absorptions at 7.4δ (singlet, 5H), 6.2δ (multiplet, 2H), 5.2δ (singlet, 2H), 4.3δ (multiplet, 1H), 3.7δ (singlet, 3H), 3.2δ (multiplet, 2H), 2.6δ (multiplet, 4H), 1.5δ (multiplet, 2H), and 0.9δ (triplet, 3H). A molecular ion at m/e 336 was observed in the mass spectrum of the product.

$C_{17}H_{24}N_2O_5$ Calculated: C, 60.71; H, 7.14; N, 8.33.

Found: C, 60.88; H, 7.20; N, 8.35.

Preparation of N^5-Substituted β-Glutamines

N^5-Benzyl β-Glutamine. The previously described procedure for the hydrogenolysis of N-benzyl- and N-phenyl carbobenzoxy glutamine was followed for the hydrogenolysis of carbobenzoxy β-glutamines also. In 200 ml. of hot ethanol was dissolved 2.0 g. (5.4 mole) of N-benzyl carbobenzoxy-β-glutamine. The solution was placed in a 300 ml. pressure bottle and 10 ml. of water and 0.3 g. of 10 percent palladium on carbon catalyst were added. The solution was treated overnight with hydrogen at a gauge pressure of 50 psi., then was filtered to remove the catalyst. The filtered catalyst was washed with water, and the filtrate was placed on a rotary evaporator to remove the solvent. The white solid which remained was dissolved in a minimum amount of hot water and a five-fold excess of methanol was added. The solution was thoroughly chilled, then was filtered to give 0.90 g. (71 percent yield) of white crystals, m. p. 207-208°.

The IR spectrum of the product showed absorptions at 1640 cm^{-1} (strong), C=O stretch and at 1550 cm^{-1} (strong), carboxylate anion stretch. When determined in trifluoroacetic acid, the NMR spectrum gave absorptions at 7.4δ (singlet, 5H), 4.5δ (doublet, 2H), 4.3δ (broad, 1H), and 3.0δ (multiplet, 4H). No molecular ion was present in the mass spectrum of the material, but a peak corresponding to m-18 was observed.

$C_{12}H_{15}N_2O_3$ Calculated: C, 61.00; H, 6.83; N, 11.86.

Found: C, 61.11; H, 6.88; N, 11.78.

N^5-Propyl β-Glutamine. In 200 ml. of hot 95 percent ethanol was dissolved 6.0 g. (0.019 mole) of N-propyl carbobenzoxy-β-glutamine. The solution was placed in a 300 ml. pressure bottle and 0.30 g. of 10 percent palladium on carbon catalyst was added. The solution was treated overnight with hydrogen at a gauge pressure of 50 psi. Enough water was added to dissolve all of the solid which had formed, and the catalyst was separated by filtration. Removal of the solvent followed by recrystallization from aqueous ethanol gave 3.95 g. (93 percent yield) of the desired product, m. p. 204-205°.

The IR spectrum contained important absorptions at 3300 cm^{-1} (strong), N-H stretch; 1640 cm^{-1} (strong), C=O stretch; and 1560 cm^{-1} (strong), carboxylate anion stretch. The NMR spectrum, obtained in D_2O, showed absorptions at 3.8δ (multiplet, 1H), 3.2δ (triplet, 2H), 2.6δ (multiplet, 4H), 1.5δ (multiplet, 2H), and 0.9δ (triplet, 3H). A molecular ion was present in the mass spectrum at m/e 188.

$C_8H_{16}N_2O_3$ Calculated: C, 51.06; H, 8.51; N, 14.89.
Found: C, 51.13; H, 8.57; N, 14.80.

Preparation of β-Glutamine Ethyl Ester Acetate Salt

In a 300 ml. pressure bottle were placed 25 ml. of absolute ethanol, 2.5 ml. of acetic acid, 3.0 g. (0.017 mole) of β-iminoglutaramic ethyl ester, and 0.4 g. of platinum oxide catalyst. The solution was treated with hydrogen at a gauge pressure of 50 psi. for four hours. The catalyst was filtered and the ethanol was removed on a rotary evaporator. To the colorless oil which remained was added 200 ml.

of diethyl ether, resulting in a formation of a turbid white solution. After being thoroughly chilled, the solution was filtered to give a white solid, m. p. 48-50°. The solid was twice crystallized from acetone to give 0.5 g. (13 percent yield) of light pink solid, m. p. 67-69°.

Significant IR absorptions were noted at 1710 cm^{-1} and 1660 cm^{-1} (strong), C=O stretch; and at 1550 cm^{-1} (strong), carboxylate anion stretch. The NMR spectrum (in acetone-d_6) showed absorptions at 3.5δ (quartet, 2H), 2.9δ (multiplet, 1H), 1.9δ (doublet, 4H), 1.3δ (singlet, 3H), and 0.6δ (triplet, 3H). No molecular ion was present in the mass spectrum.

$C_9H_{18}N_2O_5$ Calculated: C, 46.11; H, 7.69; N, 11.97.

Found:* C, 46.05; H, 7.91; N, 12.00.

Synthesis of α-Carbobenzoxyaminoglutarimides

Preparation of α-Carbobenzoxyaminoglutarimide

This product was best prepared by the method of Ose and Takamatsu (32). In a 50 ml. Erlenmeyer flask was placed 2.0 g. (0.007 mole) of carbobenzoxyglutamine. The flask was immersed for 30 minutes in an oil bath which was maintained at 190° for the duration of the heating. The resulting oil was cooled and dissolved in boiling ethanol. The solution was decolorized by treatment of the boiling solution with cocoanut charcoal then enough water to create a slight turbidity was added.

* Performed by Galbraith Laboratories, Knoxville, Tennessee.

After thorough chilling, the solution was filtered to give 1.04 g. of white solid. The solid was recrystallized from a minimum amount of isopropyl alcohol to give 0.80 g. (43 percent yield) of white crystals, m. p. 132-133° lit. (32) m. p. 129-131°. Yields of similar reactions ranged from 20-40 percent, in close agreement with reported yields.

Using the method of Kirsanov and Zolotov, the desired product was prepared in 6 percent yield by heating 10 ml. of a pyridine solution containing 2.81 g. (0.010 mole) of carbobenzoxyglutamic acid and 1.15 g. (0.012 mole) of sulfamide for a period of three hours on a steam bath. The product obtained from this reaction was not completely pure, m. p. 117-119°, but an IR spectrum was identical to the spectrum of a known sample of α-carbobenzoxyglutarimide. Other attempts to produce the cyclic product involved heating the carbobenzoxyglutamine in acetic anhydride for a one hour period and treatment of carbobenzoxyglutamine methyl ester with sodium methoxide in methanol. Both of these latter procedures failed to lead to the isolation of any of the desired product.

Attempted Preparation of N-Benzyl α-Carbobenzoxyaminoglutarimide

The attempted preparation of this compound used the method of Chemie Grünenthal (10). In a 250 ml. round-bottomed flask fitted with a Soxhlet extractor containing magnesium sulfate were placed 2.0 g. (5.4 moles) of N-benzyl carbobenzoxyglutamine and 120 ml. of p-xylene. The magnetically stirred solution was refluxed 48 hours then was concentrated to a volume of 25 ml. The solution was

thoroughly chilled and an oily product separated and partly crystallized. The xylene was decanted and the residue was recrystallized twice from ethanol-hexane to give 0.18 g. (10 percent yield) of a white crystalline solid, m. p. 140-140.7°. Yields of other reactions were as high as 40 percent. An analysis indicated that the product had resulted from the loss of a water molecule from the starting material.

$C_{20}H_{20}N_2O_4$	Calculated:	C, 68.15; H, 5.72; N, 7.95.
	Found:	C, 68.02; H, 5.76; N, 8.01.

The product was determined to contain a five-membered imide ring from its NMR and IR spectra. The IR spectrum contained carbonyl absorptions at 1745 cm^{-1} (strong) and 1670 cm^{-1} (strong), C=O stretch. The NMR spectrum contained absorptions at 7.8δ (singlet, 5H), 7.7δ (singlet, 5H), 6.7δ (broad, 1H), 5.2δ (singlet, 2H), 4.5δ (broad, 1H), 4.4δ (doublet, 2H), and 2.3δ (multiplet, 4H). The mass spectrum showed a molecular ion at m/e 352.

Several other methods of preparing this compound were attempted with little or no success. Heating the N-benzyl carbobenzoxyglutamine at 190° for one to two hours gave a small amount of the above product which was contaminated with impurities, most of the starting material being recovered unchanged. Attempts to cyclize N-benzyl carbobenzoxyglutamine methyl ester in methanol using sodium methoxide as base generally led to nearly quantitative recovery of the starting

ester. Treating the N-benzyl carbobenzoxyglutamine with thionyl chloride and triethylamine in dimethylformamide also failed to give the corresponding glutarimide derivative, as evidenced by the lack of an IR spectrum containing the necessary carbonyl absorptions for a six membered imide.

One reaction, although it did not produce the desired product, gave several new products which were able to be separated and identified. In this reaction, 10 g. (0.036 mole) of carbobenzoxyglutamic acid was added to 120 ml. of acetic anhydride and the solution was heated on a steam bath for 30 minutes. The solution was cooled and the acetic anhydride was removed on a flash evaporator, leaving a light brown oil. The oil was treated with 4 g. (.037 mole) of benzyl amine, liberating some heat from the ensuing reaction. The flask containing the reaction mixture was immersed in an oil bath maintained at 230° for three hours. The reaction mixture was cooled overnight, dissolved in 20 ml. of benzene, and chromatographed on a 200 g. column of neutral alumina.

Elution of the various bands was effected by using, in order, one liter of benzene, two liters of a 1:1 mixture of benzene-ethyl acetate, and one liter of ethyl acetate. Three fractions of interest were collected and identified.

The first component of interest which was eluted was 0.9 g. of white solid which was subsequently identified as the N-benzyl diamide of carbobenzoxyglutamic acid, m. p. 213-214°.

Important IR absorptions were observed at 3300 cm^{-1} (strong),

N-H stretch; 1680 cm^{-1} (strong) and 1640 cm^{-1} (strong), C=O stretch; and 1530 cm^{-1} (strong), N-H bend. Absorptions in an NMR spectrum obtained in pyridine-d_5 appeared at 6.5δ (singlet, 10H), 6.4δ (singlet, 5H), 4.4δ (singlet, 2H), 4.1δ (broad, 2H), 3.8δ (multiplet, 4H), and 1.9δ (broad, 4H). The mass spectrum contained a small molecular ion at m/e 459.

$C_{26}H_{29}N_3O_4$ Calculated: C, 70.58; H, 6.32;
N, 9.15.
Found: C, 70.55; H, 6.44;
N, 9.18.

The second eluted product of interest was 1.1 g. of a product identified as N-benzyl N^1-[3-(1-benzylglutarimido)]urea, m. p. 175-176° after recrystallization from ethyl acetate-hexane. The compound was assigned a 5-membered ring structure on the basis of IR absorptions at 1765, 1700, and 1635 cm^{-1} corresponding to C=O stretching absorptions of a cyclic 5-membered imide, an acyclic urea, and an acyclic secondary amide respectively. The NMR of the product in pyridine-d_5 showed absorptions at 6.5δ (doublet, 5H), 6.4δ (doublet, 5H), 4.0δ (singlet, 2H), 3.8δ (doublet, 2H), 3.6δ (multiplet, 1H), and 1.8δ (broad multiplet, 4H).

$C_{20}H_{21}N_3O_3$ Calculated: C, 68.34; H, 6.03;
N, 11.96.
Found: C, 68.22; H, 6.20;
N, 11.95.

The third product isolated from the reaction mixture was 0.6 g. of N^7-benzyl pyroglutamamide, m. p. 140-141°, lit. (3) m. p. 134-136°, after recrystallization from ethyl acetate-hexane. The product had IR absorptions at 1665 and 1650 cm^{-1}, attributed to the carbonyl absorptions of a lactam and a monosubstituted amide. The proposed identification of the product was supported by an analysis, but was not completely confirmed.

$C_{12}H_{14}N_2O_2$	Calculated:	C, 66.05; H, 6.42; N, 12.84.
	Found:	C, 66.76; H, 6.41; N, 12.71.

The compound was found to have a molecular ion in its mass spectrum. An exact mass determination was obtained and verified the proposed formula.

Exact mass calculated:	218.1052 amu.
Exact mass found:	218.1054 amu.

Attempted Preparation of N-Phenyl α-carbobenzoxyaminoglutarimide

Several attempts were made to cyclize N-phenyl carbobenzoxyisoglutamine to the 6-membered imide structure, but the desired product was never isolated. In one attempt 3 g. (8.4 mmole) of N-phenyl carbobenzoxyisoglutamine was placed in a 50 ml. Erlenmeyer flask and the flask was immersed for 1.5 hours in an oil bath maintained at 195°. The flask and its contents were cooled and 75 ml. of chloroform was

added, dissolving the solid in the flask. The solution was extracted twice with 10 percent sodium hydroxide solution and then once with water. Acidification of the extracts gave a small amount of the starting material. The chloroform solution was dried over magnesium sulfate and the solvent was removed on a rotary evaporator, leaving a tan oil. The oil was crystallized from ethanol-hexane, then the product was recrystallized twice from isopropyl alcohol to give 50 mg. of white solid, m. p. 175-177°. An IR spectrum of the product had an absorption at 1780 cm^{-1}, possibly indicating a cyclic 5-membered imide instead of the desired 6-membered cyclic imide. An analysis did not give the hoped-for results.

$C_{19}H_{18}N_2O_4$	Calculated:	C, 67.46; H, 5.33; N, 8.28.
	Found:	C, 68.75; H, 5.73; N, 8.66.

The further purification and identity of the product was not pursued since the IR had indicated the desired product was not formed in the reaction.

Refluxing the isoglutamine derivative in xylene for four days using the method of Chemie Grünenthal (10) gave the same product as heating the material at 190°. Again the product was not completely purified as it could never be crystallized, although an IR spectrum of the oil formed in the reaction was identical to that of the previously discussed reaction product.

The last method attempted for the synthesis of N-phenyl α-carbobenzoxyaminoglutarimide was that of Clayton, Skinner, and Shepherd (11). In a flask equipped with a magnetic stirrer and a calcium chloride drying tube were placed 3.60 g. (0.10 mole) of N-phenyl carbobenzoxyisoglutamine and 30 ml. of dry N, N-dimethyl formamide. The solution was treated with 0.8 ml. (11.2 mmole) of thionyl chloride and 1.50 ml. (11.2 mmole) of triethylamine. After the solution had stirred at room temperature for one hour, another 1.50 ml. of triethylamine was added. The solution was stirred another hour, then was filtered to remove the triethylamine hydrochloride. The resulting solution was stripped of solvent on a rotary evaporator, leaving a brown oil. The oil was dissolved in ethyl acetate and the ensuing solution was extracted, in order, with dilute hydrochloric acid, 10 percent sodium hydroxide, dilute hydrochloric acid, and water. The solution was dried over magnesium sulfate and the solvent was removed on a rotary evaporator, leaving a yellow oil. The oil was crystallized from ethanol-hexane, then was recrystallized from isopropyl alcohol-hexane to give 1.0 g. of white solid, m. p. 110-112°. Further recrystallization did not decrease the melting point range. An analysis of the product did not support the desired structure.

$C_{19}H_{18}N_2O_4$	Calculated:	C, 67.46; H, 5.33; N, 8.28.
	Found:	C, 66.70; H, 6.26; N, 7.70.

An IR of the product contained C=O carbonyl absorptions at 1780 cm^{-1}, indicating that the compound possibly contained a cyclic 5-membered imide. The structure of the product of this reaction was never determined, and the attempted synthesis of N-phenyl α-carbobenzoxy-aminoglutarimide was finally abandoned to concentrate of the synthesis of β-carbobenzoxyaminoglutarimide derivatives.

Synthesis of β-Carbobenzoxyaminoglutarimide Derivatives

Preparation of β-Carbobenzoxyaminoglutarimide

The procedure of Clayton, Skinner, and Shepherd (11) was found to be the most successful method of preparation of the β-carbobenzoxy-aminoglutarimides reported in this work. In an Erlenmeyer flask protected by a calcium chloride drying tube and fitted with a magnetic stirrer were placed 1.40 g. (5.0 mmole) of carbobenzoxy-β-glutamine and 15 ml. of dry N,N-dimethyl formamide. When the solid had dissolved 0.4 ml. (5.0 mmole) of thionyl chloride and 0.75 ml. of triethylamine (5.0 mmole) was added. After stirring for one hour, another 0.75 ml. of triethylamine was added to the solution. The solution was stirred an additional hour then the triethylamine hydrochloride was removed by filtration. After addition of one ml. of water, the solution was placed on a rotovap and the solvent was removed. The dark oil which remained was dissolved in ethyl acetate. This solution was extracted with dilute hydrochloric acid, 5 percent sodium bicarbonate solution, and water, then was dried over magnesium sulfate. The ethyl acetate was removed on a rotary evaporator to give a pale yellow oil. The oil was crystallized from ethanol-hexane to give 0.46

g. of yellow solid, m. p. 123-126°. The product was recrystallized twice from isopropyl alcohol to give 0.30 g. (23 percent yield) of a light tan powder, m. p. 125-126°.

The IR spectrum contained significant absorptions at 3400 cm^{-1} (medium), N-H stretch, 1700 cm^{-1} (strong); C=0 stretch; and 1530 cm^{-1} (strong), N-H bend. The NMR spectrum, obtained in acetone-d_6 contained bands at 9.6δ (broad, 1H), 7.4δ (singlet, 5H), 6.8δ (broad, 1H), 5.2δ (singlet, 2H), 4.3δ (multiplet, 1H), 2.9δ (singlet, 2H), and 2.8δ (doublet, 2H). The mass spectrum contained a molecular ion at m/e 262.

$C_{13}H_{14}N_2O_4$ Calculated: C, 59.54; H, 5.34;
N, 10.69.
Found: C, 59.31; H, 5.41;
N, 10.57.

Attempts to cyclize the starting material by refluxing in xylene for four days or by heating at 190° for two hours led to recovery of the starting material. None of the desired product was isolated from either of the reaction mixtures.

Preparation of N-Propyl β-Carbobenzoxyaminoglutarimide

In a 100 ml. Erlenmeyer flask protected by a calcium chloride drying tube were placed 50 ml. of dry N,N-dimethyl formamide and 1.61 g. (5.0 mmole) of N-propyl carbobenzoxy-β-glutamine. The solution was treated with 0.45 ml. (5.1 mmole) of thionyl chloride and 0.75 ml. (5.1 mmole) of triethyl amine, then after stirring one hour was treated with another 0.75 ml. of triethylamine. The solution was

stirred one hour after the last triethylamine addition, then 10 ml. of water was added and the solution was stripped of solvent on a rotary evaporator. The residue was dissolved in ethyl acetate and the resulting solution was extracted with water, dilute hydrochloric acid, and 5 percent sodium bicarbonate solution. The ethyl acetate was dried over magnesium sulfate and was removed using a rotary evaporator, leaving a dark, oily residue. The oil was recrystallized twice from isopropyl alcohol to give 35 mg. (3 percent yield) of white solid, m. p. 90-91°. It seems likely that much of the product was lost during the recrystallization steps.

Significant absorptions in the IR spectrum occurred at 3350 cm^{-1} (strong, N-H stretch; 1710 cm^{-1} (strong), C=O stretch; 1665 cm^{-1} (strong), C=O stretch, and 1530 cm^{-1} (strong), N-H bend. The NMR spectrum obtained in deuterochloroform contained absorptions at 7.3δ(singlet, 5H), 5.5δ (doublet, 1H), 5.0δ (singlet, 2H), 4.1δ (multiplet, 1H), 3.7δ (triplet, 2H), 2.8δ (triplet, 4H), 1.5δ (quartet, 2H), 0.8δ (triplet, 3H). The mass spectrum contained a molecular ion at m/e 304.

$C_{16}H_{20}N_2O_4$	Calculated:	C, 63.16; H, 6.58; N, 9.21.
	Found:	C, 63.23; H, 6.68; N, 9.16.

Heating the N-propyl carbobenzoxy-β-glutamine at 210° for 15 minutes was also found to give the desired product, although the product was not completely purified. Attempts to cyclize the starting material

by refluxing in acetic anhydride for four hours or in xylene for four days proved unsuccessful, unreacted starting material being recovered in each case.

Preparation of N-Benzyl β-Carbobenzoxyaminoglutarimide

The exact procedure described for the two preceding cyclization reactions was used with no changes. Starting with 1.85 g. (5.0 mmole) of N-benzyl carbobenzoxy-β-glutamine, 0.67 g. (42 percent yield) of a white solid, m. p. 105-106°, was prepared. The desired imide structure was indicated by an analysis and spectra of the compound.

The IR spectrum contained major absorptions at 3400 cm^{-1} (medium), N-H stretch; 1715 cm^{-1} and 1670 cm^{-1} (strong), C=O stretch; and 1535 cm^{-1} (strong), N-H bend. Absorptions in the NMR spectrum were observed at 7.3δ (singlet, 5H), 7.2δ (singlet, 5H), 5.2δ (singlet, 1H), 5.1δ (singlet, 2H), 4.9δ (singlet, 2H), 4.0δ (broad, 1H), and 2.8δ (triplet, 4H). A molecular ion at m/e 352 was present in the mass spectrum.

$C_{20}H_{20}N_2O_4$ Calculated: C, 68.15; H, 5.72; N, 7.95.

Found: C, 68.37; H, 5.66; N, 7.93.

Sulfonamide Derivatives of Substituted Glutamines

Preparation of N^2-(p-Nitrobenzenesulfonyl)glutamine

This product was prepared using the procedure of Ose and Takamatsu (31). To a solution of 40 g. (0.47 mole) of sodium bicarbonate

in 600 ml. of water was added 32 g. (0.21 mole) of L-(+)-glutamine. When the glutamine had dissolved, 56 g. (0.25 mole) of p-nitrobenzenesulfonyl chloride was added over a one hour period. The solution was stirred for 21 hours at room temperature, then was filtered and acidified with concentrated hydrochloric acid. The solution was thoroughly chilled and was filtered to give a large amount of white crystals. The solid was recrystallized from water-ethanol to give 31 g. (43 percent yield) of white needles, m. p. 169-170°, lit. (31) m. p. 170-172°.

The IR spectrum contained absorptions at 1700 cm^{-1} (strong) and 1650 cm^{-1} (strong), C=O stretch, 1520 cm^{-1} (strong) and 1350 cm^{-1} (strong), C-NO_2; and 1160 cm^{-1} (strong), S=O stretch. The NMR spectrum obtained in pyridine-d_5 showed absorptions at 8.8δ (broad singlet, 3H), 7.4δ (singlet, 4H), 3.8δ (multiplet, 1H), and 1.8δ(multiplet, 4H). A molecular ion was not present in the mass spectrum.

Preparation of N-(p-Nitrobenzenesulfonylglutamine) Ethyl Ester

In an adaptation of the method of Taschner and Wasielewski (45), 3.31 g. (0.01 mole) of N-(p-nitrobenzenesulfonyl)glutamine was added to 100 ml. of ethyl acetate. After the addition of one ml. of concentrated sulfuric acid the solution was allowed to stir at room temperature for 48 hours. The solid dissolved slowly during this period until it had all dissolved. The solution was transferred to a separatory funnel and was extracted with 100 ml. of saturated sodium bicarbonate solution. After separating the two layers, the aqueous layer was extracted with ethyl acetate. The ethyl acetate solutions were combined, dried over magnesium sulfate, and evaporated to dryness

on a rotary evaporator. The residual white solid was recrystallized from an ethanol-water solution to give 1.1 g. (30 percent yield) of white product, m. p. 169-170°.

Absorptions occurred in the IR spectrum at 3380 cm^{-1} (strong), N-H stretch; 1720 cm^{-1} (strong) and 1650 cm^{-1} (strong), C=O stretch; 1520 cm^{-1} (strong) and 1350 cm^{-1} (strong), C-NO_2; and 1310 cm^{-1} (strong) and 1160 cm^{-1} (strong), S=O stretch. The NMR spectrum (in acetone-d_5) contained bands at 7.7δ (quartet, 4H), 7.0δ (broad, 1H), 3.3δ (multiplet, 3H), 2.1δ (singlet, 2H), 1.6δ (multiplet, 4H), and 0.4δ (triplet, 3H). The mass spectrum did not contain a molecular ion, but contained a peak at m-45.

$C_{13}H_{17}N_3O_7S$	Calculated:	C, 43.45; H, 4.74;
		N, 11.70; S, 8.91.
	Found:*	C, 43.58; H, 4.75;
		N, 11.53; S, 8.95.

Preparation of N^2-(N-acetylsulfanilyl)glutamine

Following the general procedure of Ose and Takamatsu (31), 32 g. (0.21 mole) of L-(+)-glutamine and 58 g. (0.25 mole) of N-acetylsulfanilyl chloride were reacted in sodium bicarbonate solution for four hours at room temperature to give, after recrystallization from water-ethanol, 40 g. (55 percent yield) of white crystals, m. p. 185-186°.

The IR spectrum of the product contained significant absorption

* Performed by Galbraith Laboratories, Knoxville, Tennessee.

bands at 3300 cm^{-1} (strong), N-H stretch; 1720 cm^{-1} (strong), 1665 cm^{-1} (strong), and 1630 cm^{-1} (strong), C=O stretch; and 1325 cm^{-1} (strong) and 1160 cm^{-1} (strong), S=O stretch. An NMR spectrum in pyridine-d_5 showed absorptions at 10.8δ (singlet, 1H), 8.0δ (singlet, 4H), 4.6δ (broad, 1H), 2.8δ (broad multiplet, 4H), and 2.2δ (singlet, 3H). No molecular ion was observed in the mass spectrum of the product, however a peak corresponding to the loss of a water molecule was observed.

$C_{13}H_{17}N_3O_6S$	Calculated:	C, 45.48; H, 4.96;
		N, 12.24; S, 9.33.
	Found:	C, 45.33; H, 5.06;
		N, 12.02; S, 9.50.

Preparation of N-Benzyl N-(p-Nitrobenzenesulfonyl)glutamine

In 150 ml. of warm methanol was dissolved 5.0 g. (0.013 mole) of N-benzyl carbobenzoxyglutamine. The solution was placed in a 300 ml. pressure bottle and 0.5 g. of 10 percent palladium on carbon catalyst was added. The solution was treated with hydrogen on a Parr hydrogenation apparatus overnight at an initial gauge pressure of 50 psi. The catalyst was filtered and the solvent was removed on a rotovap to give 3.2 g. of crude N-benzyl glutamine, m. p. 125-128°. The solid was dissolved in 75 ml. of hot pyridine. The resulting solution was cooled to 45° and 4.0 g. (0.024 mole) of p-nitrobenzenesulfonyl chloride was added. The clear orange solution was cooled to room temperature and was stirred overnight. The solution was then poured into 100 ml. of cold water and was acidified with hydrochloric acid. After being

chilled overnight, the solution was filtered to give 1.80 g. (33 percent yield) of light yellow solid, m. p. 201-205°. A small portion of the product was recrystallized twice from an ethanol-water solution, raising the melting point to 217-218°.

An IR spectrum showed absorptions at 1720 cm^{-1} (strong) and 1650 cm^{-1} (strong), C=O stretch; 1530 cm^{-1} (strong) and 1350 cm^{-1} (strong), C-NO_2; and 1320 cm^{-1} (medium) and 1170 cm^{-1} (strong), S=O stretch. No NMR spectrum was recorded for the product. The mass spectrum contained a small molecular ion at m/e 421.

$C_{18}H_{19}N_3O_7S$	Calculated:	C, 51.31; H, 4.51; N, 9.98; S, 7.60.
	Found:	C, 51.29; H, 4.63; N, 9.90; S, 7.72.

Preparation of N-Phenyl N-(p-Nitrobenzenesulfonyl)isoglutamine

In 200 ml. of ethanol was dissolved 6.0 g. (0.017 mole) of N-phenyl carbobenzoxyisoglutamine. The solution was placed in a pressure bottle and 0.3 g. of 10 percent palladium on carbon catalyst was added. The solution was treated with hydrogen at 50 psi overnight then the catalyst was filtered and the solvent was removed on a rotary evaporator. The residual solid was dissolved in 50 ml. of 1.0 N NaOH solution and 4.0 g. (0.024 mole) of p-nitrobenzenesulfonyl chloride was added. The solution was stirred for two and one-half hours at room temperature after which it was acidified with hydrochloric acid. Filtration of the acidified solution gave 0.90 g. of brown solid, m. p. 166-169°.

Upon recrystallization from ethanol-water solution, 0.52 g. (8 percent yield) of pale yellow solid was obtained, m. p. 192-193°.

Absorption bands occurred in the IR spectrum at 1700 cm^{-1} (strong) and 1630 cm^{-1} (strong), C=O stretch; 1540 cm^{-1} (strong) and 1350 cm^{-1} (strong), C-NO_2; and 1320 cm^{-1} (strong) and 1180 cm^{-1} (strong), S=O stretch. No molecular ion was observed in the mass spectrum, but a peak was observed at m-18.

$C_{17}H_{17}N_3O_7S$	Calculated:	C, 50.12; H, 4.18;
		N, 10.32; S, 7.86.
	Found:	C, 50.05; H, 4.19;
		N, 10.30; S, 7.71.

Sulfonamide Derivatives of β-Glutamic Acid

Preparation of p-Nitrobenzenesulfonyl-β-glutamic Acid

The method of Wagner and Wagner-Jauregg (47) was followed for this reaction. In 320 ml. of 1.0 N sodium hydroxide solution was dissolved 14.7 g. (0.10 mole) of β-glutamic acid. The solution was heated to 55° and 26.5 g. (0.12 mole) of p-nitrobenzenesulfonyl chloride was added over a period of 20 minutes. The solution was stirred at 55° for two hours then was filtered to remove undissolved reactants. The filtrate was acidified with concentrated hydrochloric acid and, after thorough chilling, was filtered to give 6.0 g. of light green solid, m. p. 191-196°. The product was recrystallized twice from water to give 3.35 g. (10 percent yield) of light yellow solid, m. p. 204-205°.

The IR spectrum of the product contained bands at 1700 cm^{-1} (strong), C=O stretch; 1520 cm^{-1} (strong) and 1340 cm^{-1} (strong), $C-NO_2$; and 1160 cm^{-1} (strong), S=O stretch. Absorption bands in the NMR spectrum, obtained in dimethylsulfoxide-d_6, were found at 10.0δ (broad, 1H), 8.4δ (quartet, 4H), 4.0δ (broad, 1H), and 2.6δ (doublet, 4H). No molecular ion was present in the mass spectrum.

$C_{11}H_{12}N_2O_8S$ Calculated: C, 39.76; H, 3.61;
N, 8.43; S, 9.64.
Found: C, 39.87; H, 3.68;
N, 8.51; S, 9.76.

Attempted Preparation of N^3-(p-Nitrobenzenesulfonyl)-β-glutamine

In 200 ml. of warm ethanol was dissolved 3.0 g. (0.011 mole) of carbobenzoxy-β-glutamine. The solution was added to a 300 ml. pressure bottle containing 0.2 g. of 10 percent palladium on carbon catalyst, then was treated with hydrogen at a gauge pressure of 50 psi for 16 hours. The catalyst was filtered and the solvent was stripped on a rotary evaporator, leaving a white solid. The material was dissolved in 25 ml. of 1.0 N sodium hydroxide solution and 2.2 g. (0.010 mole) of p-nitrobenzenesulfonyl chloride was added. The solution was stirred at room temperature for two hours, then was acidified with hydrochloric acid. The desired sulfonamide did not precipitate, even upon prolonged cooling of the solution. Attempts to concentrate the solution on a rotary evaporator failed to lead to the isolation of any product whose IR spectrum contained both

sulfonamide S=O stretching absorptions and carbonyl C=O absorptions.

The extreme lack of solubility of the β-glutamine in pyridine precluded the use of that solvent as a possible reaction medium.

Attempted Preparation of N-Propyl p-Nitrobenzenesulfonyl-β-glutamine

The above described procedure for the attempted preparation of p-nitrobenzenesulfonyl-β-glutamine was followed exactly, using the same weights of reactants. Once again no product could be obtained which had an IR spectrum corresponding to the expected spectrum of the desired product. The same lack of solubility of the β-glutamine derivative in pyridine also eliminated that solvent as a potential reaction medium.

Attempted Preparation of N^5-Benzyl p-Nitrobenzenesulfonyl-β-glutamine

Attempts similar to those described above were made to condense p-nitrobenzenesulfonyl chloride with N-benzyl β-glutamine in 1.0 N sodium hydroxide solution. Unfortunately, none of these attempts gave a product whose structure looked promising as the desired product. An attempt was also made to prepare the desired sulfonamide by use of hot pyridine as a reaction solvent, but the N-benzyl β-glutamine was insoluble even in the hot pyridine and no products of the reaction were identified. No further efforts were made at this time to prepare the N-benzyl p-nitrobenzenesulfonyl-β-glutamine.

Attempted Preparation of N^3-(N-Acetylsulfanilyl)-β-glutamine Ethyl Ester

A procedure similar to that of Ose and Takamatsu (31) was employed for this reaction. The product from the reduction of 4.0 g. (0.023 mole) of β-iminoglutaramic ethyl ester in the presence of 5 ml.

(0.09 mole) of acetic acid was dissolved in 55 ml. (0.135 mole) of 10 percent sodium hydroxide solution at room temperature. To the stirred solution was added 7.0 g. (0.30 mole) of N-acetylsulfanilyl chloride resulting in a 10° temperature rise. The solution was stirred two hours at room temperature, then was filtered to remove unreacted sulfonyl chloride. The solution was acidified with concentrated hydrochloric acid and was thoroughly chilled. No precipitated material was observed after three days, so the solution was concentrated to one-half its original volume.

Filtration of the resulting solution led to the isolation of 0.4 g. of sulfanilic acid, identified by comparison of an IR spectrum of the material with that of a known sample. Further concentration of the reaction solution led to the isolation of a total of 7 g. of crude sulfanilic acid. No product containing sulfonamide S=O abosrptions was isolated from the reaction mixture.

The use of pyridine as a solvent for the desired reaction and/or the use of p-nitrobenzenesulfonyl chloride in place of N-acetylsulfanilyl chloride failed to give any product whose IR spectrum showed absorptions due to sulfonamide, ester carbonyl and amide carbonyl absorptions in one molecule. Attempts to synthesize the product by this procedure were eventually abandoned.

Synthesis of Sulfonamide Derivatives of Aminoglutarimides

Preparation of α-(p-Nitrobenzenesulfonylamido)-glutarimide

This material was first prepared by the heating of p-nitrobenzenesulfonylglutamine. This method of preparing glutarimide

derivatives is well documented in the literature (33, 34). In a 50 ml. Erlenmeyer flask was placed 4.5 g. (0.014 mole) of p-nitrobenzene-sulfonyl glutamine. The flask was immersed for 15 minutes in an oil bath maintained at 180°. The white solid melted, forming a dark blue liquid. The flask was removed from the oil bath and was allowed to cool. The resulting solid was broken up and added to 300 ml. of tetrahydrofuran which contained 8 g. of cocoanut charcoal. The solution was heated and refluxed for four hours. The charcoal was removed by filtration and the tetrahydrofuran was taken off on a rotary evaporator, leaving a green oil which was crystallized by addition of 20 ml. of water and subsequent cooling. The 4.0 g. of crude product thus obtained was recrystallized from a hot solution of 70 ml. of dioxane and 500 ml. of water to give 1.0 g. (24 percent yield) of pale yellow solid, m. p. 239-240°.

The IR spectrum contained major absorptions at 3300 cm^{-1} (strong), N-H stretch; 1720 cm^{-1} and 1690 cm^{-1} (strong), C=O stretch; 1520 cm^{-1} (strong) and 1360 cm^{-1} (shoulder), C-NO_2; and 1340 cm^{-1} (strong), and 1160 cm^{-1} (strong), S=O stretch. When determined in pyridine-d_5, the NMR spectrum showed bands at 7.6δ (singlet, 4H), 4.0δ (multiplet, 1H), 2.1δ (multiplet, 2H), and 1.7δ (multiplet, 2H). The mass spectrum showed a molecular ion at m/e 313.

$C_{11}H_{11}N_3O_6S$ Calculated: C, 42.17; H, 3.51; N, 13.42; S, 10.22.

Found:* C, 42.34; H, 3.62; N, 13.53; S, 10.42.

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* Performed by Galbraith Laboratories, Knoxville, Tennessee.

This product was also prepared using the general procedure of Sondheimer and Holley (39). A cold ethanol solution of p-nitrobenzenesulfonylglutamine ethyl ester was prepared by dissolving 1.44 g. (0.004 moles) of the ester in 35 ml. of boiling ethanol, then cooling the solution to 0° in an ice-bath. This solution was added at 0° to a solution, also at 0°, of 0.184 g. (0.008 mmole) of freshly cut sodium in 10 ml. of ethanol. Mixing of the two solutions gave a clear yellow solution, however, after approximately 15 seconds the solution became turbid and remained that way for the duration of the reaction. The solution was stirred at 0° for 40 minutes, then was acidified with 2 ml. of glacial acetic acid. The acidification caused the solution to become clear once again. The solution was added to 40 ml. of water, causing no immediate result. After several minutes, a white precipitate began to appear. After thorough chilling the solution was filtered to give 0.86 g. (69 percent yield) of product, m. p. 230-233°. An IR spectrum of the product was identical to a spectrum of α-(p-nitrobenzenesulfonylamido)-glutarimide prepared by the previously described procedure.

The product was also prepared in 9.0 percent yield by refluxing 1.0 g. (3.0 mole) of p-nitrobenzenesulfonylglutamine in 11 ml. of glacial acetic acid for one hour. The product, m. p. 240-241°, was isolated by thoroughly chilling and filtering the reaction solution after heating was complete.

Preparation of α-(N-Acetylsulfanilamido)glutarimide

This material was originally prepared by the first procedure

described above for the preparation of α-(p-nitrobenzenesulfonylamido)-glutarimide. In a 50 ml. Erlenmeyer flask was placed 3.0 g. (8.8 mmole) of N-acetylsulfanilglutamine. The flask was immersed for 20 minutes in an oil bath maintained at 180°. The solid melted to a greenish black oil. The flask and its contents were cooled, and the solidified product was removed and crushed in a mortar. The powder was dissolved in 400 ml. of boiling dioxane. The solution was cooled below refluxing temperature, 15 g. of cocoanut charcoal was added, and the solution was heated to boiling again. After being refluxed for two hours, the solution was filtered to remove the charcoal and the dioxane was stripped on a rotovap, leaving a yellow solid. The solid was recrystallized twice from 30 percent ethanol to give 0.20 g. (7.0 percent yield) of white crystalline product, m. p. 270-271°.

Significant absorption bands in the IR spectrum were observed at 3350 cm^{-1} (strong), 3250 cm^{-1} (strong), and 3150 cm^{-1} (strong), N-H stretch; 1700 cm^{-1} (strong) and 1665 cm^{-1} (strong), C=O stretch; 1530 cm^{-1} (strong) and 1360 cm^{-1} (strong), C-NO_2; and 1320 cm^{-1} (strong) and 1160 cm^{-1} (strong), S=O stretch. The NMR spectrum obtained in pyridine-d_5 contained absorptions at 7.3δ (doublet, 4H), 3.8δ (multiplet, 1H), 1.9δ (multiplet, 2H), 1.5δ(multiplet, 2H), and 1.3δ (singlet, 3H). A molecular ion at m/e 325 was observed in the mass spectrum of the product.

$C_{13}H_{15}N_3O_5S$ Calculated: C, 48.00; H, 4.62; N, 12.92; S, 9.85.

Found: C, 48.14; H, 4.69; N, 12.88; S, 9.96.

The product was also prepared from α-carbobenzoxyaminoglutarimide by the following procedure. In a 50 ml. Erlenmeyer flask was placed 2.5 g. (9.6 mmole) of α-carbobenzoxyaminoglutarimide. To this solid was added 15 ml. of a 30 percent hydrogen bromide in acetic acid solution, causing evolution of carbon dioxide. After five minutes, the solution was poured into 150 ml. of diethyl ether, resulting in the formation of an insoluble oil in the solution. The ether was decanted and 100 ml. of acetone was added, causing the oil to crystallize. The solution was filtered to give 1.35 g. (67 percent yield) of crude α-aminoglutarimide hydrobromide, m. p. 273°d.

The hydrobromide was dissolved in 7 ml. of dry pyridine and 0.9 ml. (6.4 mmole) of triethylamine was added. The solution was cooled to room temperature and 1.60 g. (6.9 mmole) of N-acetylsulfanilyl chloride was added. The solution was protected with a calcium chloride drying tube and was stirred 20 hours at room temperature. The solution was poured into 100 ml. of iced-water with vigorous stirring. After several minutes a precipitate was evident in the solution. After thorough chilling, the solution was filtered to give 1.50 g. of product, m. p. 268-270°. Recrystallization from dilute ethanol gave 1.25 g. (48 percent yield) of white, crystalline solid, m. p. 276-276.5°. An IR spectrum of the solid was identical to that of a sample of the previously prepared α-(N-acetylsulfanilamido)-glutarimide.

Attempted Preparation of N^1-Benzyl α-(p-Nitrobenzenesulfonamido)-glutarimide

In 200 ml. of methanol was dissolved 2.0 g. (5.4 mmole) of N-benzyl α-carbobenzoxyaminoglutarimide. The solution was bubbled for 5 minutes with hydrogen chloride gas then was treated with hydrogen at 50 psi for 12 hours in the presence of 10 percent palladium on carbon catalyst. The catalyst and solvent were removed, leaving a brown oil which was subsequently dissolved in pyridine to give a green solution. To the solution was added 1.5 g. (6.8 mmole) of p-nitrobenzenesulfonyl chloride, resulting in a two degree temperature rise. After being stirred overnight, the solution was added to 150 ml. of water and the resulting solution was thoroughly chilled. Filtration gave 0.22 g. of green solid, m. p. 134-140°. The product was recrystallized from ethanol-water to give 50 mg. of grey solid, m. p. 185-187°. An IR spectrum of the material showed all necessary absorptions for the desired product. Attempts to recrystallize the material another time led to the loss of all of the product. When a second reaction failed to give the product as expected, the attempted synthesis was curtailed due to a lack of starting material.

The same product, identified by its IR spectrum, was produced when N-benzyl carbobenzoxyglutamine was refluxed in xylene for four days. Starting from 1.2 g. of the glutamine, three milligrams of impure product was isolated. No attempt was made to further purify the product due to the poor recovery yields encountered previously.

Preparation of N^1-Benzyl β-(p-Nitrobenzenesulfonylamido)-glutarimide

In a 300 ml. pressure bottle was placed 0.55 g. (1.55 mmole) of N-benzyl β-carbobenzoxyaminoglutarimide, 50 ml. of ethanol, and 0.1 g. of 10 percent palladium on carbon catalyst. The solution was shaken with hydrogen overnight at a gauge pressure of 50 psi. The catalyst was filtered off and the solvent was removed on a rotary evaporator, leaving a colorless oil which slowly turned dark blue. The oil was dissolved in 10 ml. of dry pyridine and 0.46 g. (2.0 mmole) of p-nitrobenzenesulfonyl chloride was added. The solution was protected by a calcium chloride drying tube while stirring for eight hours at room temperature. The reaction solution was poured into an iced solution of hydrochloric acid, giving an immediate precipitate. After thorough chilling, 0.50 g. of tan solid was isolated by filtration. The product was recrystallized from ethanol to give 0.27 g. (43 percent yield) of light brown solid, m. p. 219-220°.

The IR spectrum of the product contained absorption bands at 1725 cm^{-1} (strong) and 1660 cm^{-1} (strong), C=O stretch; 1530 cm^{-1} (strong) and 1360 cm^{-1} (strong), $C-NO_2$; and 1320 cm^{-1} (strong) and 1160 cm^{-1} (strong), S=O stretch. An NMR spectrum obtained in acetone-d_6 showed bands at 8.8δ (quartet, 4H), 7.3δ (singlet, 5H), 4.9δ (singlet, 2H), 4.1δ (broad, 1H), 2.9δ (multiplet, 5H). The mass spectrum contained a molecular ion at m/e 403.

$C_{18}H_{17}N_3O_6S$ Calculated: C, 53.60; H, 4.22; N, 10.42; S, 7.94.

Found: C, 53.75; H, 4.21; N, 10.42; S, 7.83.

Preparation of New Sulfanilamide Derivatives

N^5-Benzyl Sulfanilylglutamine

In 150 ml. of warm ethanol was dissolved 0.85 g. (2.0 mmole) of N-benzyl N-(p-nitrobenzenesulfonyl)glutamine. After addition of 0.2 g. of 10 percent palladium on carbon catalyst, the solution was treated for one hour with hydrogen at 50 psi gauge pressure on a Parr apparatus. The uptake of hydrogen had ceased after four minutes of shaking. The catalyst was filtered and the ethanol was removed on a rotovap, leaving a colorless oil which soon crystallized. The product was recrystallized from water to give 0.70 g. (89 percent yield) of white solid, m. p. 168-169°.

Absorptions of importance in the IR spectrum were found at 3350 cm^{-1} (medium) and 3300 cm^{-1} (medium), N-H stretch; 1700 cm^{-1} (medium) and 1650 cm^{-1} (strong), C=0 stretch; 1320 cm^{-1} (medium) and 1160 cm^{-1} (strong), S=0 stretch. The NMR spectrum obtained in acetone-d_6, showed absorptions at 7.3δ (singlet, 5H), 7.2δ (quartet, 4H), 4.4δ (singlet, 2H), 4.0δ (broad, 1H), 2.4δ (multiplet, 2H), and 1.9δ (multiplet, 2H). The mass spectrum did not contain a molecular ion, but showed a peak at m-18.

$C_{18}H_{21}N_3O_5S$	Calculated:	C, 55.24; H, 5.37;
		N, 10.74; S, 8.18.
	Found:	C, 55.38; H, 5.46;
		N, 10.64; S, 8.03.

N^5-Phenyl Sulfanilylisoglutamine

In 50 ml. of ethanol was dissolved 0.41 g. (1.0 mmole) of N-phenyl N-(p-nitrobenzenesulfonyl)isoglutamine. Using palladium on carbon catalyst, the starting compound was reduced using hydrogen at an initial gauge pressure of 50 psi for a period of 30 minutes. Removal of the catalyst first and then the solvent left a white solid as a residue. The material was recrystallized from aqueous ethanol to give 0.33 g. (88 percent yield) of white product, m. p. 177-178°.

The IR spectrum contained absorptions at 3300 cm^{-1} (strong), N-H stretch; 1740 cm^{-1} (strong) and 1660 cm^{-1} (strong), C=O stretch, and 1320 cm^{-1} (strong) and 1160 cm^{-1} (strong), S=O stretch. The NMR spectrum, determined in acetone-d_6, contained bands at 7.3δ (multiplet, 9H), 4.0δ (multiplet, 1H), 2.5δ (multiplet, 2H) and 2.0δ (multiplet, 2H). No molecular ion was present in the mass spectrum.

$C_{17}H_{19}N_3O_5S$ Calculated: C, 54.11; H, 5.04;
N, 11.14; S, 8.49.
Found: C, 54.15; H, 5.17;
N, 11.15; S, 8.59.

Sulfanilyl β-Glutamic Acid

The general hydrogenation procedure described above for the preparation of sulfanilamides was again followed. From 1.0 g. (3.0 mmole) of p-nitrobenzenesulfonyl-β-glutamic acid was prepared 0.65 g. (72 percent yield) of sulfanilyl-β-glutamine, m. p. 202-203°.

Absorption bands in the IR spectrum were found at 1700 cm^{-1}

(strong), C=O stretch; and at 1320 cm^{-1} (strong) and 1160 cm^{-1} (strong), S=O stretch. The NMR spectrum obtained in acetone-d_6 contained bands at 7.3δ (quartet, 4H), 4.0δ (triplet, 1H), and 2.7δ (doublet, 4H). A small molecular ion at m/e 302 was present in the mass spectrum of the compound.

$C_{11}H_{14}N_2O_6S$	Calculated:	C, 43.71; H, 4.64;
		N, 9.27; S, 10.60.
	Found:	C, 43.77; H, 4.69;
		N, 9.29; S, 10.48.

Sulfanilyl-α-aminoglutarimide

In 80 ml. of hot dioxane was dissolved 2.0 g. (6.4 mmole) of α-(p-nitrobenzenesulfonylamido)-glutarimide. After the solution had cooled, 0.70 g. of 10 percent palladium on carbon catalyst was added. The solution was treated with hydrogen at an initial gauge pressure of 50 psi for 45 minutes on a Parr hydrogenation apparatus. When the pressure was no longer decreasing, the catalyst was removed by filtration and the solvent was evaporated, leaving a pale yellow oil. The oil was crystallized from boiling water which contained a small amount of ethanol to give 1.60 g. (88 percent yield) of yellow solid, m. p. 192-194°. A small amount of the material was recrystallized to give an analytical sample, m. p. 199-200°.

The IR spectrum contained absorptions at 1700 cm^{-1} (shoulder), and 1680 cm^{-1} (strong), C=O stretch; and 1350 cm^{-1} (strong), and 1145 cm^{-1} (strong), S=O stretch. The NMR spectrum obtained in acetone-

d_6 showed absorptions at 9.0δ (broad, 1H), 7.5δ (quartet, 4H), 5.5δ (broad, 1H), 4.8δ (broad, 2H), 3.3δ (multiplet, 1H), and 2.2δ(multiplet, 4H). The mass spectrum contained a molecular ion at m/e 283.

$C_{10}H_{13}N_3O_4S$	Calculated:	C, 46.64; H, 4.60;
		N, 14.84; S, 11.31.
	Found:	C, 46.88; H, 4.70;
		N, 14.62; S, 11.15.

CHAPTER IV

CONCLUSIONS

Attempts to prepare 4-chloroglutarimide from β-chloroglutaric acid were unsuccessful due to dehydrohalogenation of the acid when subjected to the basic conditions necessary for cyclization. Derivatives of β-carbobenzoxyaminoglutarimide were prepared from the corresponding carbobenzoxy-β-glutamine derivatives by treatment with thionyl chloride and triethylamine. Sulfonamide derivatives of aminoglutarimides can be readily prepared by the reaction of a sulfonyl chloride and the aminoglutarimide using pyridine as a solvent.

Substituted glutamine and β-glutamine derivatives may be prepared by the action of an amine on carbobenzoxyglutamic anhydride or carbobenzoxy-β-glutamic anhydride, followed by hydrogenolysis of the carbobenzoxy group. The synthesis of sulfanilamide derivatives of N^5-substituted glutamines may be effected by reaction of the appropriate glutamine with p-nitrobenzenesulfonyl chloride in pyridine, followed by catalytic reduction of the nitro group to the corresponding amine. The analogous sulfonylation employing β-glutamines does not occur in pyridine, due to a lack of solubility of the β-glutamines in that solvent.

CHAPTER V

RECOMMENDATIONS

It is felt that the β-carbobenzoxyaminoglutarimides prepared during this work could be easily converted to the corresponding sulfanilamide derivatives by procedures developed during the work. The conversion of the β-glutamine derivatives synthesized during this investigation to the sulfanilyl derivatives should likewise be readily accomplished by methods similar to the procedures reported in this investigation.

The preparation of various acylated derivatives of the β-aminoglutarimides synthesized during this investigation would be of considerable interest since many such compounds are reported to possess activity toward virus-related diseases.

It would be of interest to obtain data regarding the physiological activities of the new potential therapeutic agents which were prepared during the course of this investigation.

APPENDIX A

INFRARED SPECTRA

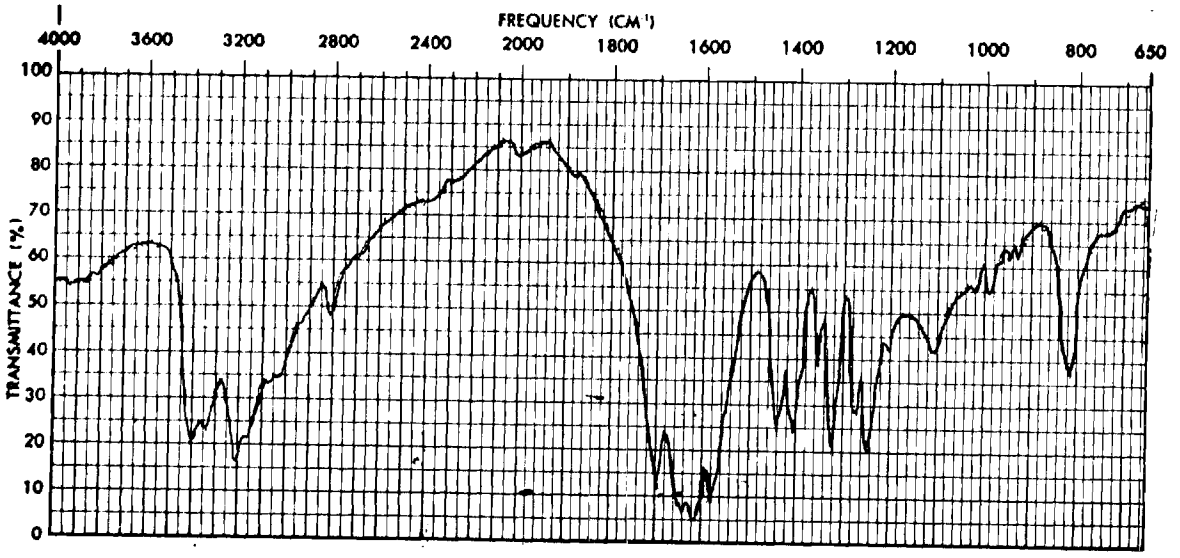


Figure 29. Infrared Spectrum of 4-Iminoglutarimide.

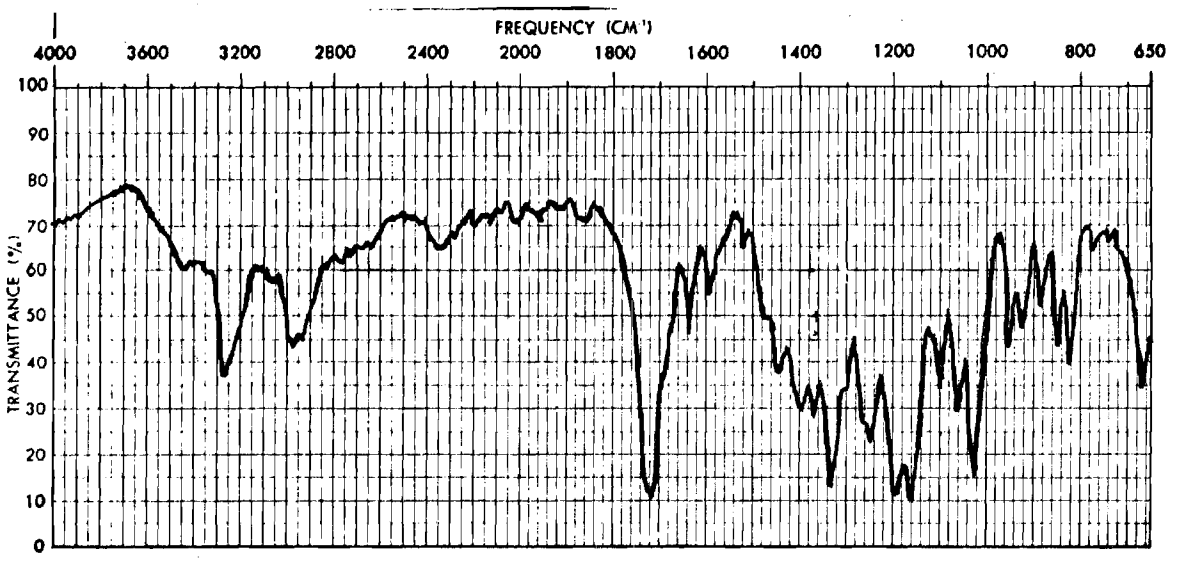


Figure 30. Infrared Spectrum of Diethyl Acetonedicarboxylate Tosylhydrazone.

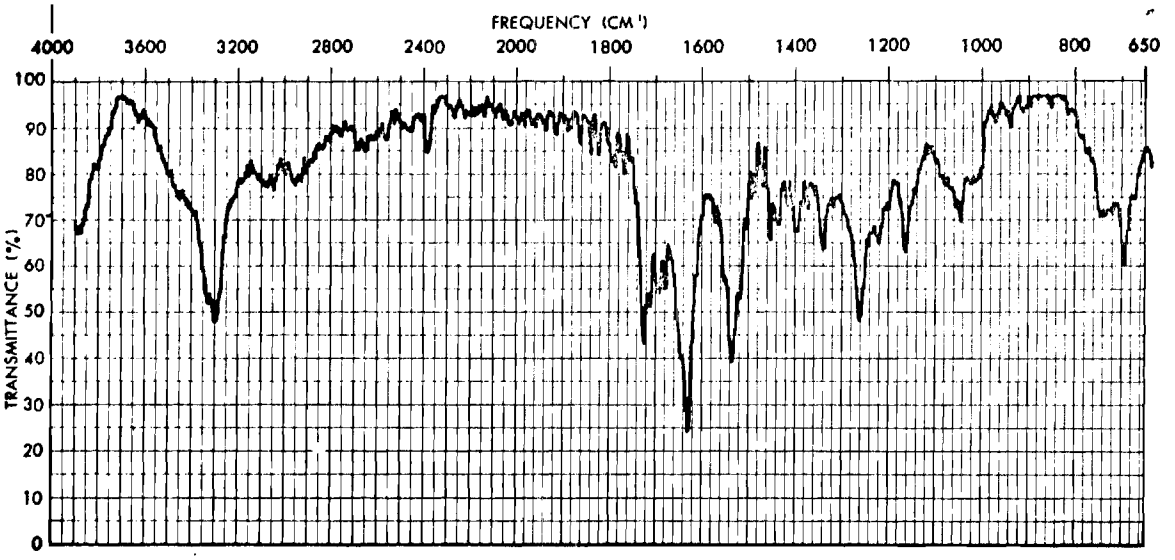


Figure 31. Infrared Spectrum of N-Benzyl Carbobenzoxyglutamine.

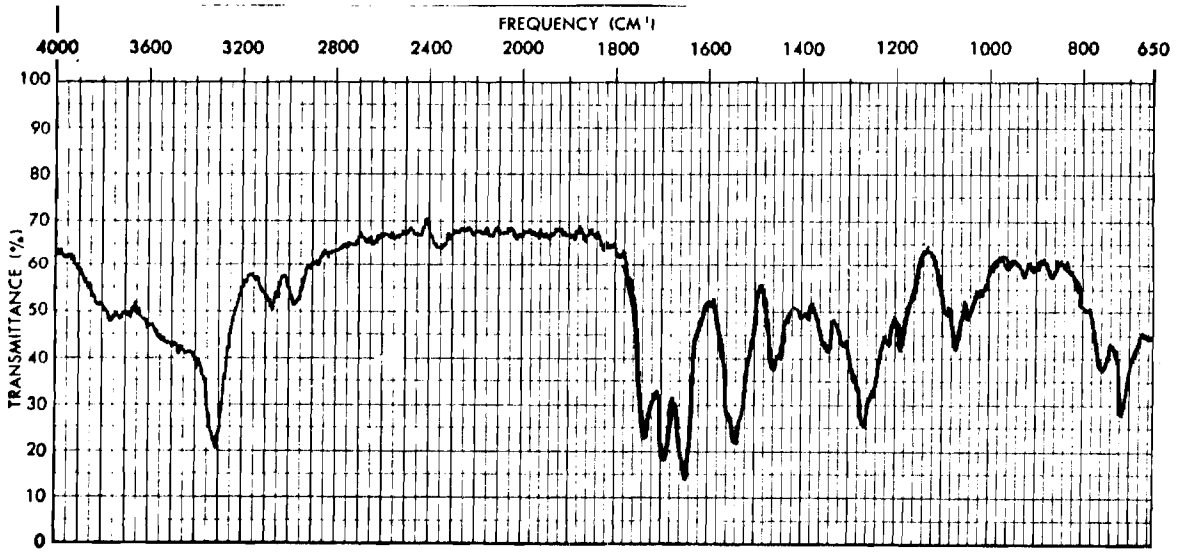


Figure 32. Infrared Spectrum of N-Benzyl Carbobenzoxyglutamine Methyl Ester.

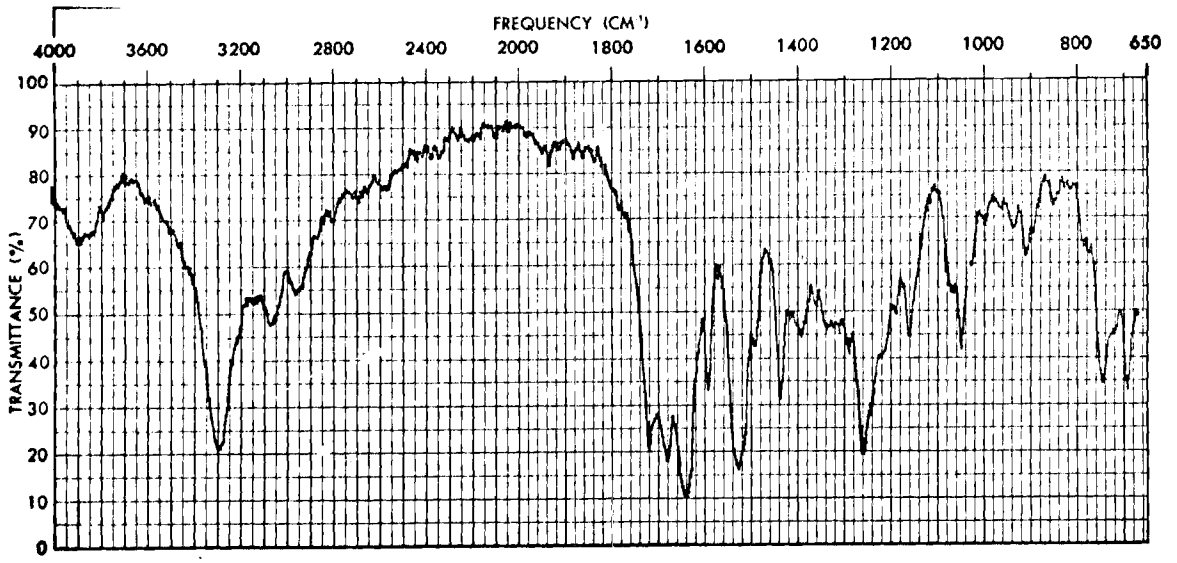


Figure 33. Infrared Spectrum of N-Phenyl Carbobenzoxyisoglutamine.

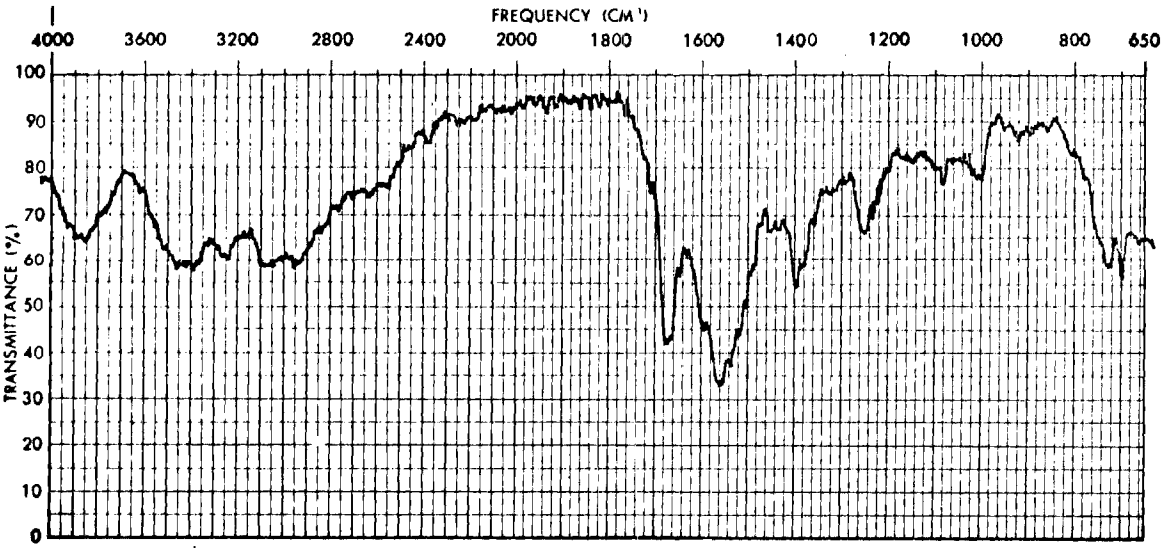


Figure 34. Infrared Spectrum of N-Benzyl Glutamine.

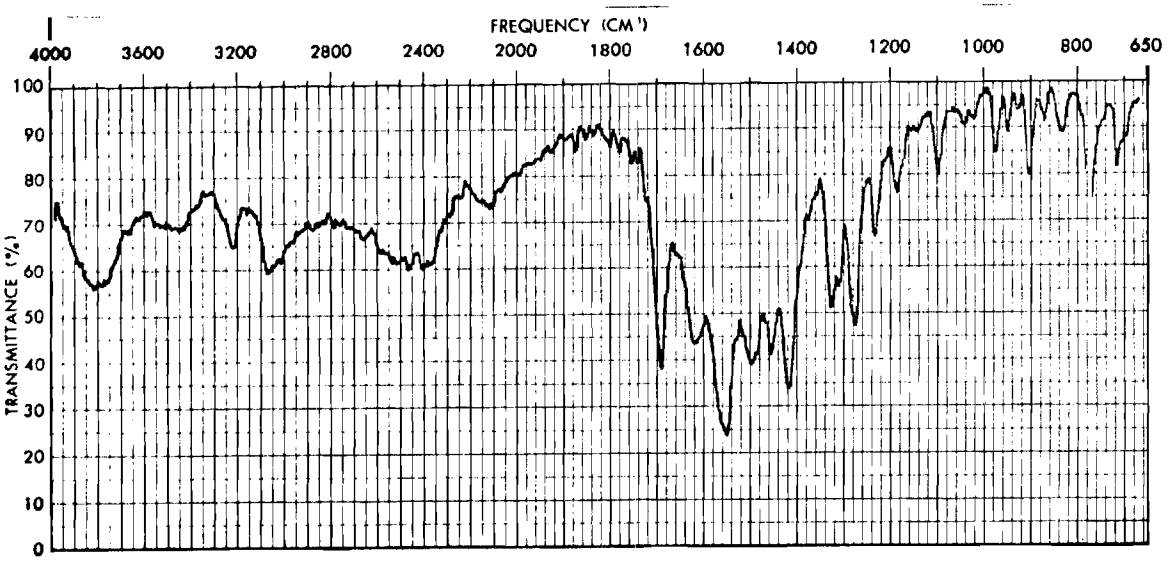


Figure 35. Infrared Spectrum of N-Phenyl Isoglutamine.

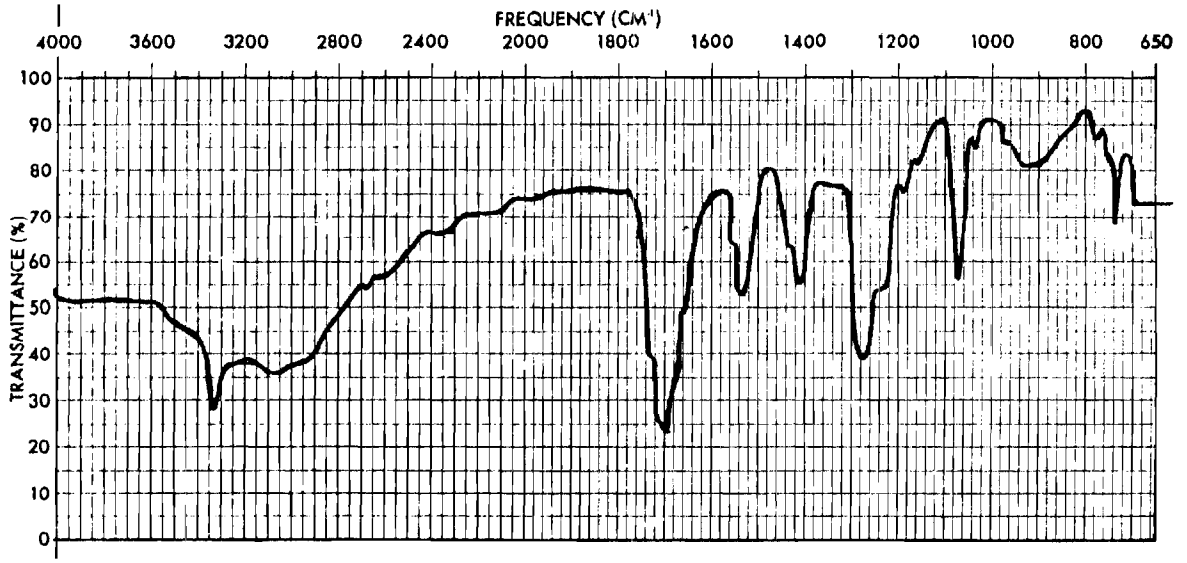


Figure 36. Infrared Spectrum of Carbobenzoxy-β-glutamic Acid.

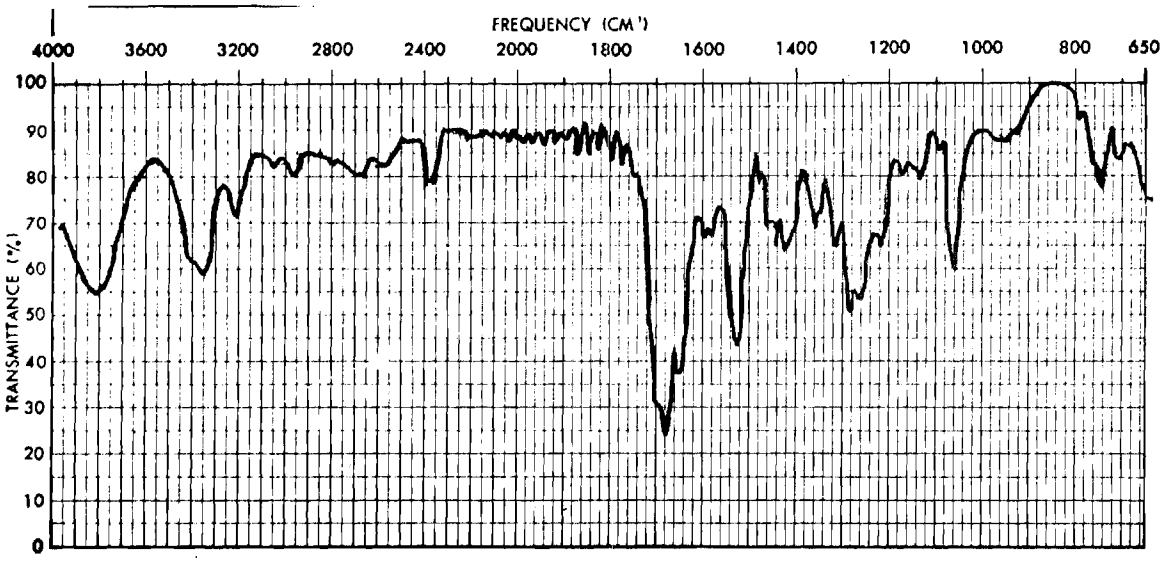


Figure 37. Infrared Spectrum of Carbobenzoxy-β-glutamine.

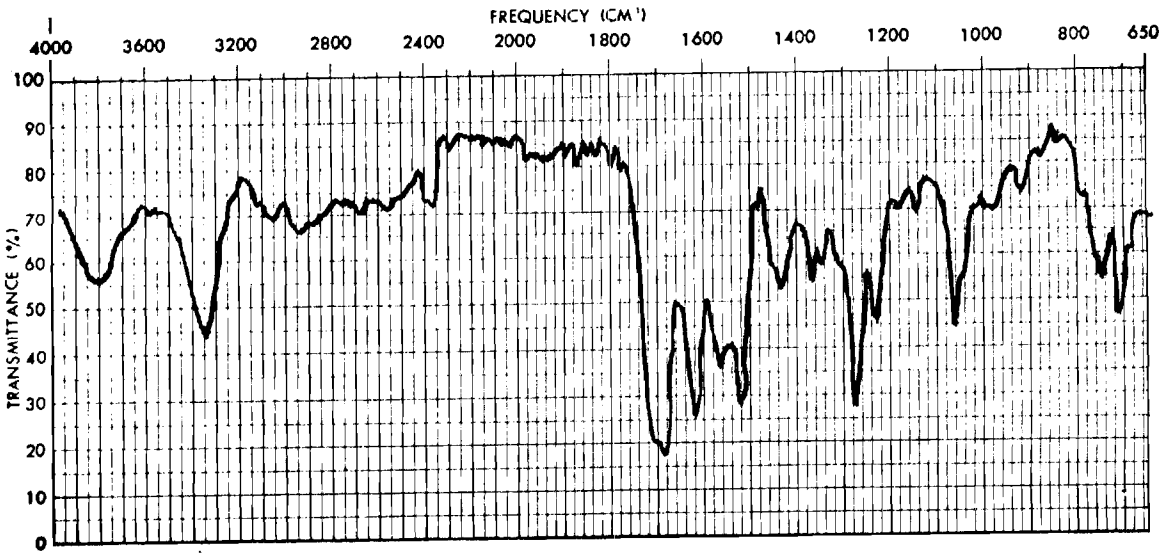


Figure 38. Infrared Spectrum of N-Benzyl Carbobenzoxy-β-glutamine.

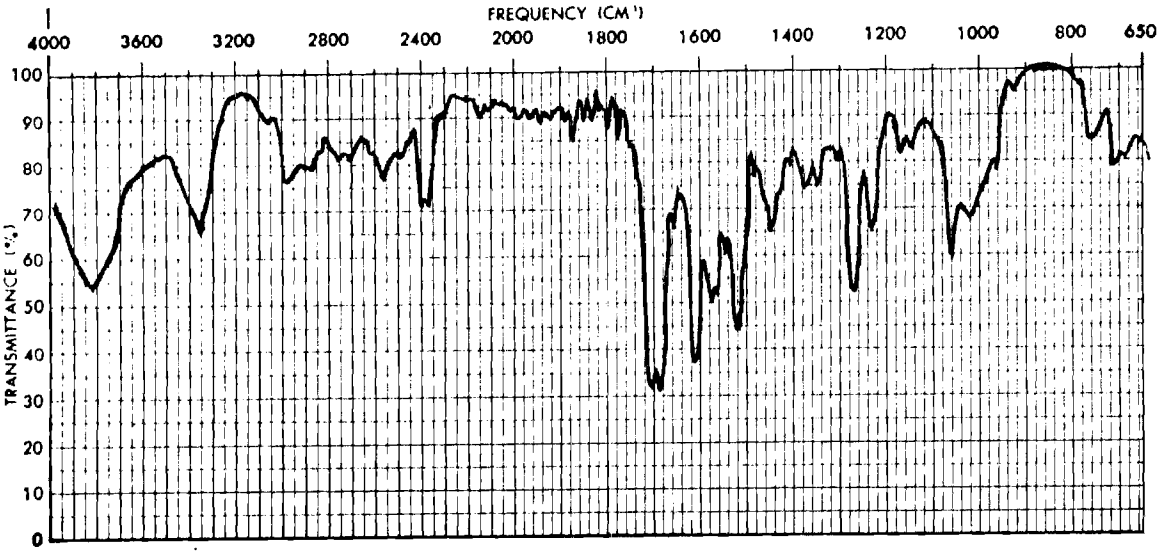


Figure 39. Infrared Spectrum of N-Propyl Carbobenzoxy-β-glutamine.

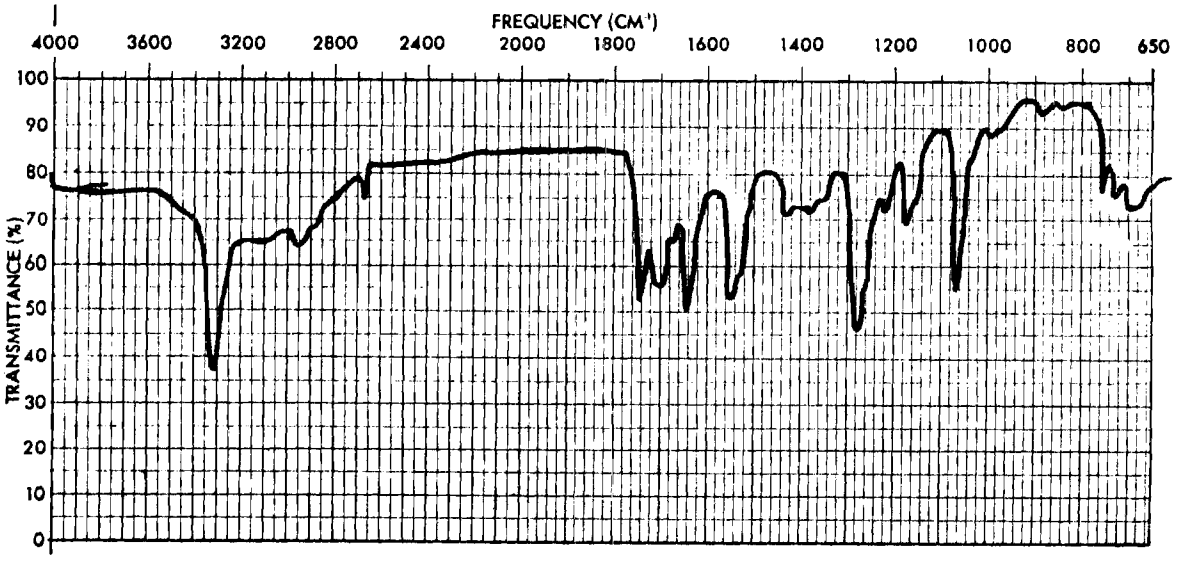


Figure 40. Infrared Spectrum of N-Propyl Carbobenzoxy-β-glutamine Methyl Ester.

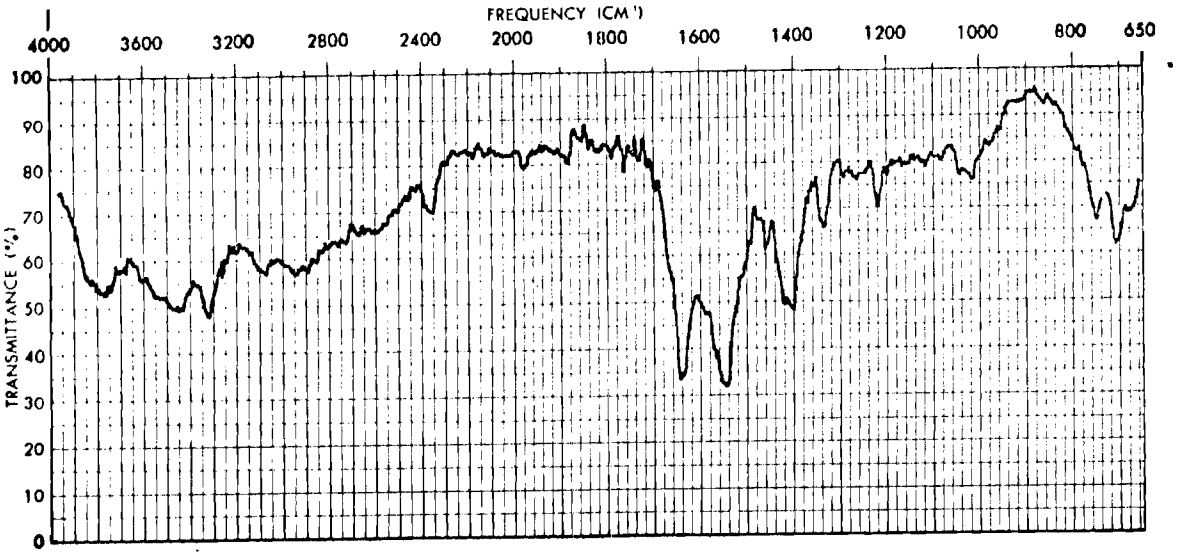


Figure 41. Infrared Spectrum of N-Benzyl β-Glutamine.

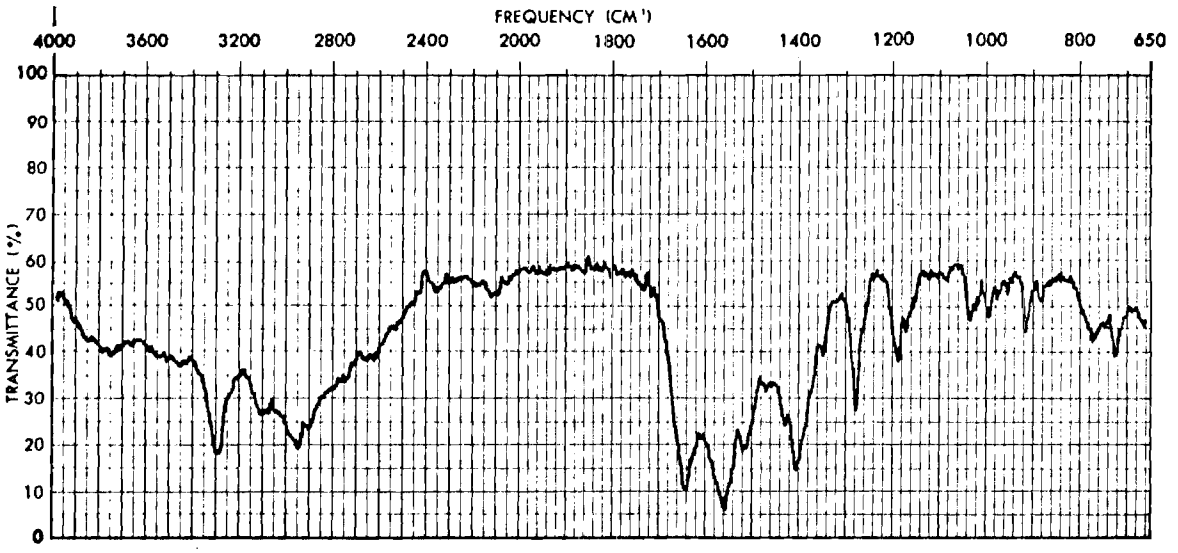


Figure 42. Infrared Spectrum of N-Propyl β-glutamine.

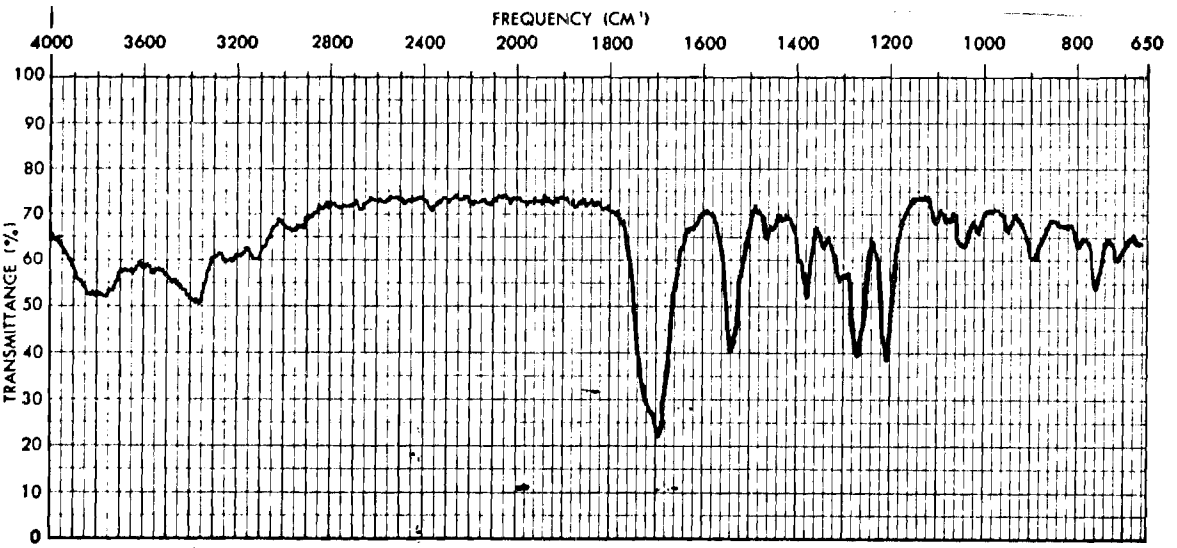


Figure 43. Infrared Spectrum of α-Carbobenzoxyaminoglutarimide.

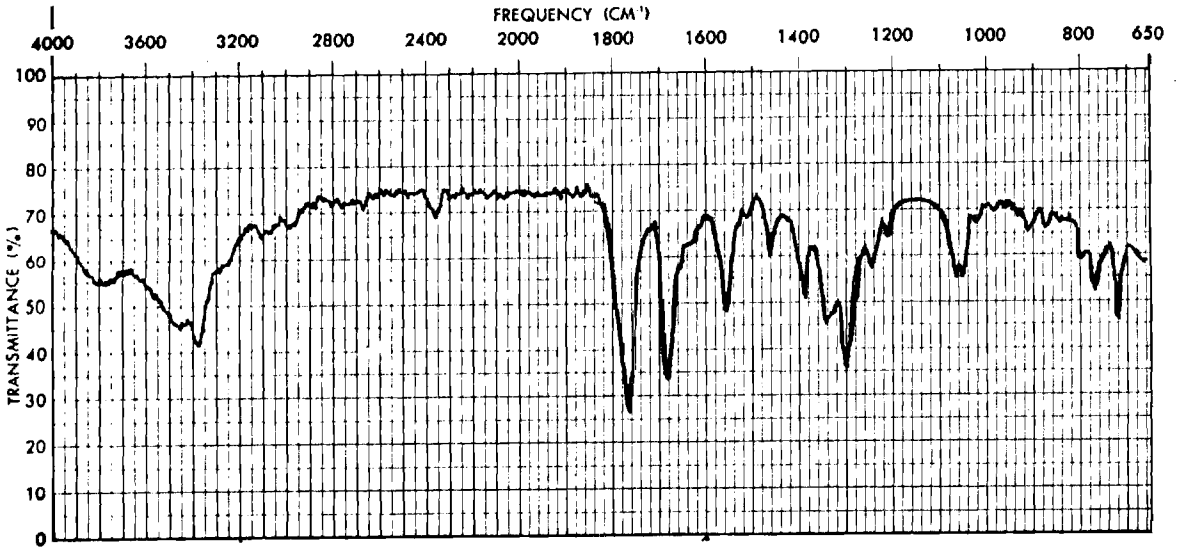


Figure 44. Infrared Spectrum of 1-Carboxybenzyl-5-(N-benzyl) carboxamide-2-pyrrolidinone.

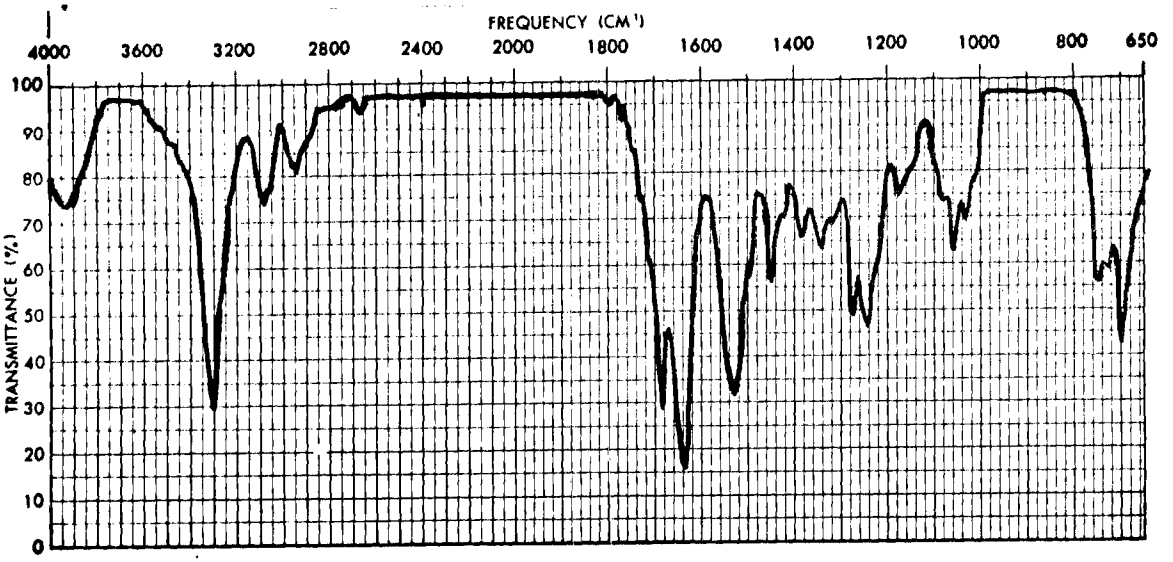


Figure 45. Infrared Spectrum of N,N'-Dibenzyl Carbobenzoxyglutamamide.

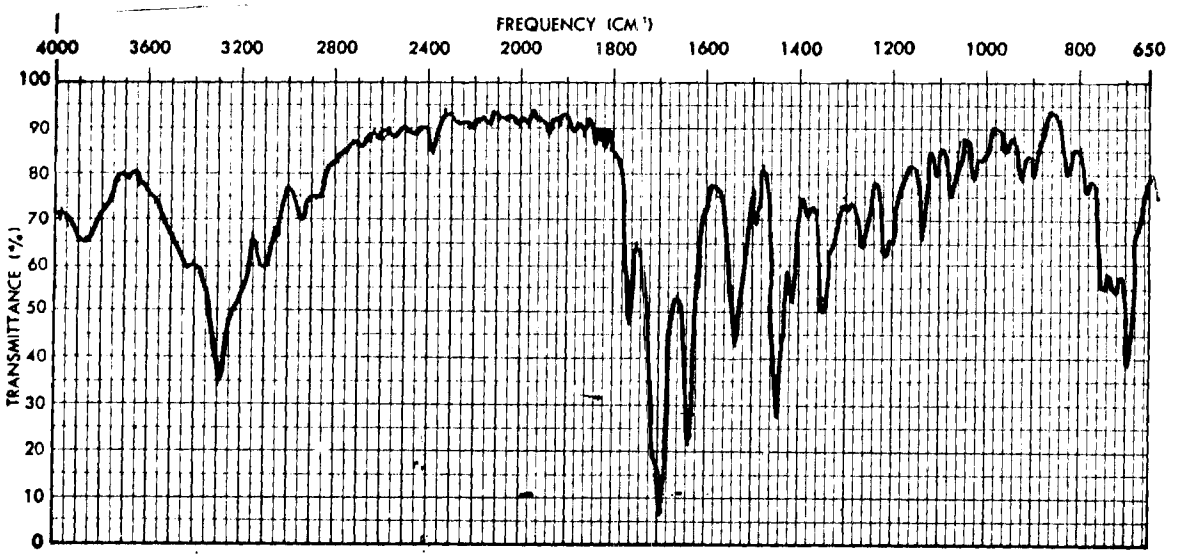


Figure 46. Infrared Spectrum of N-Benzyl N'-[3-(1-benzyl-glutarimido)] urea.

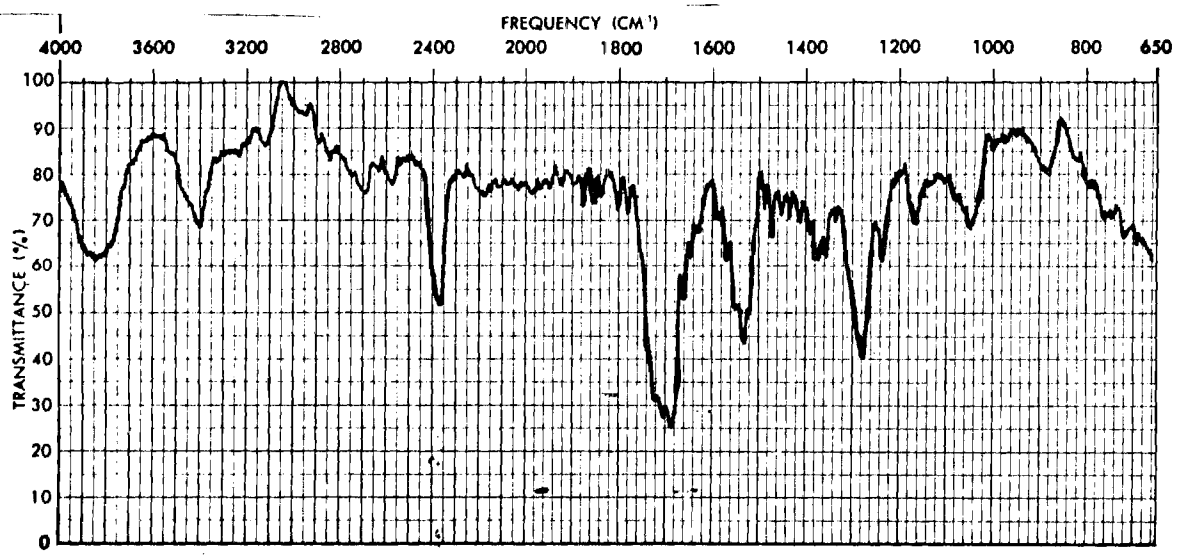


Figure 47. Infrared Spectrum of β-Carbobenzoxyaminoglutarimide.

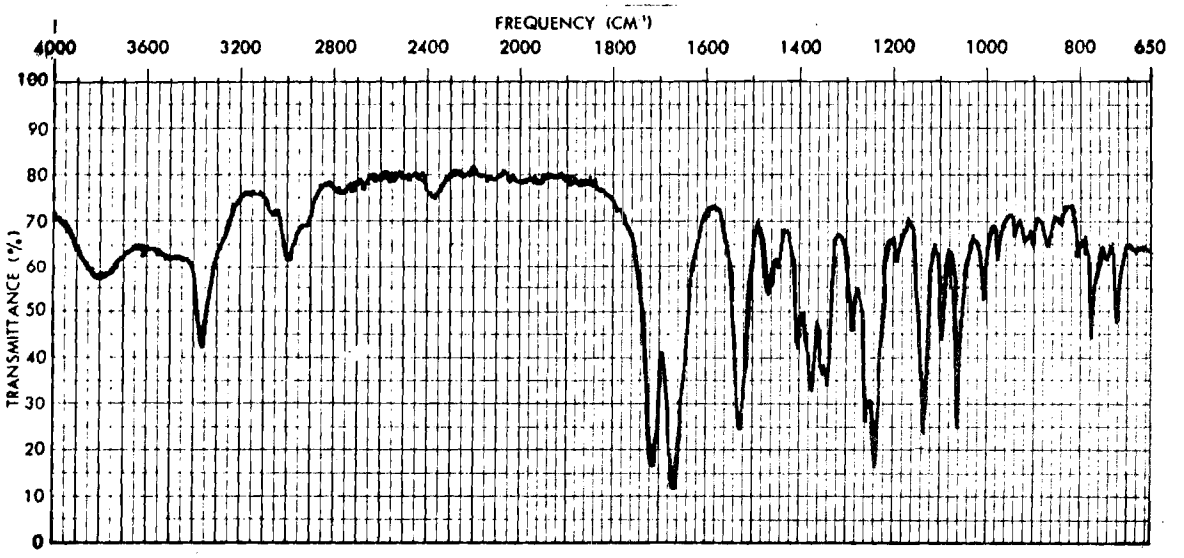


Figure 48. Infrared Spectrum of N-Propyl β-Carbobenzoxyaminoglutarimide.

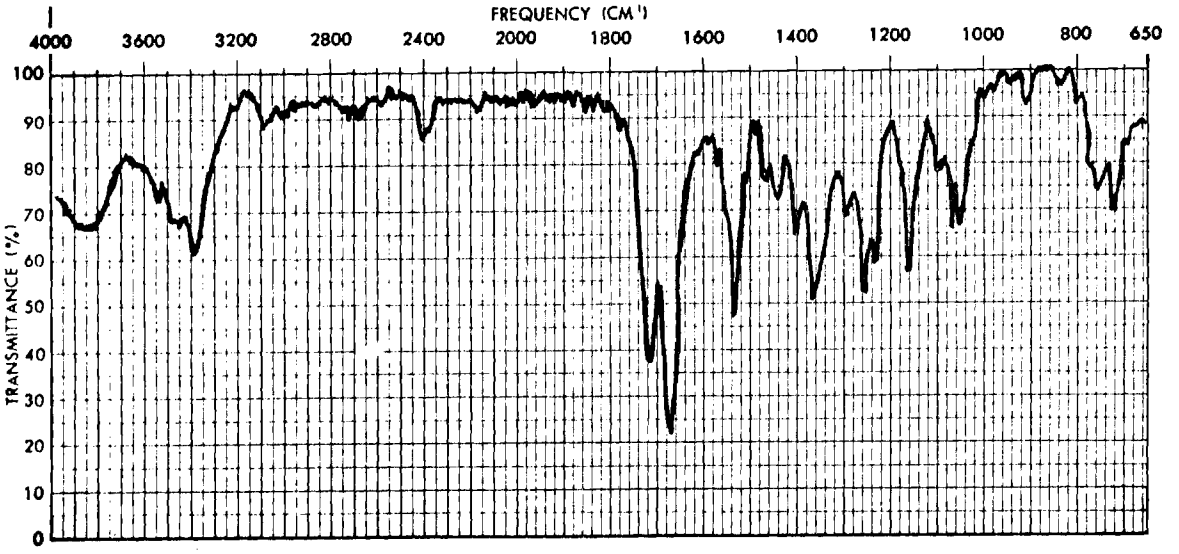


Figure 49. Infrared Spectrum of N-Benzyl β-Carbobenzoxy-aminoglutarimide.

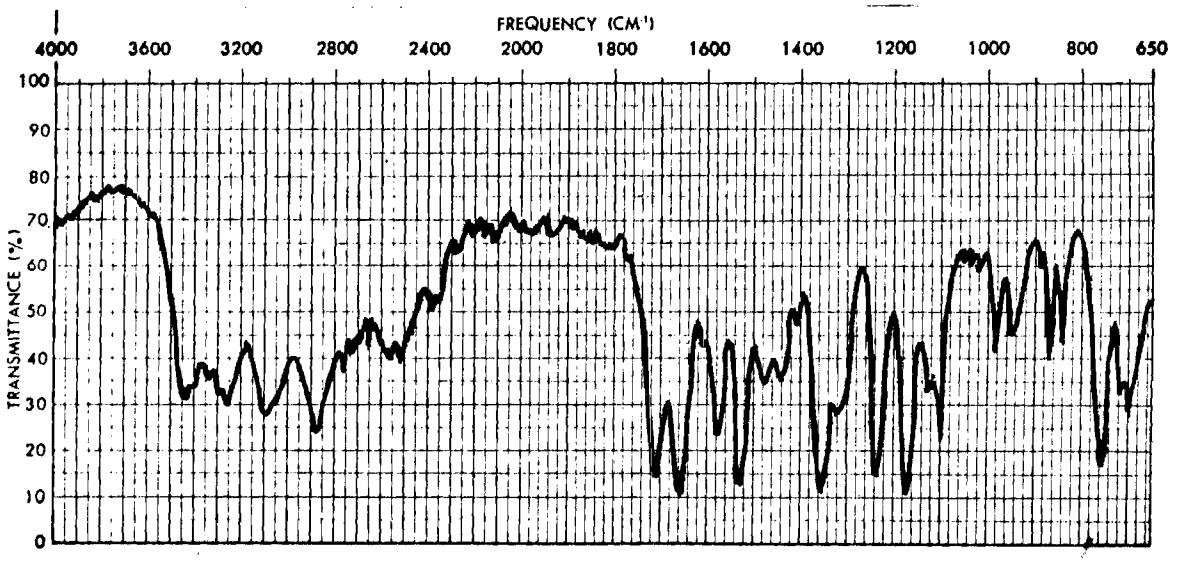


Figure 50. Infrared Spectrum of N-(p-Nitrobenzenesulfonyl)-glutamine.

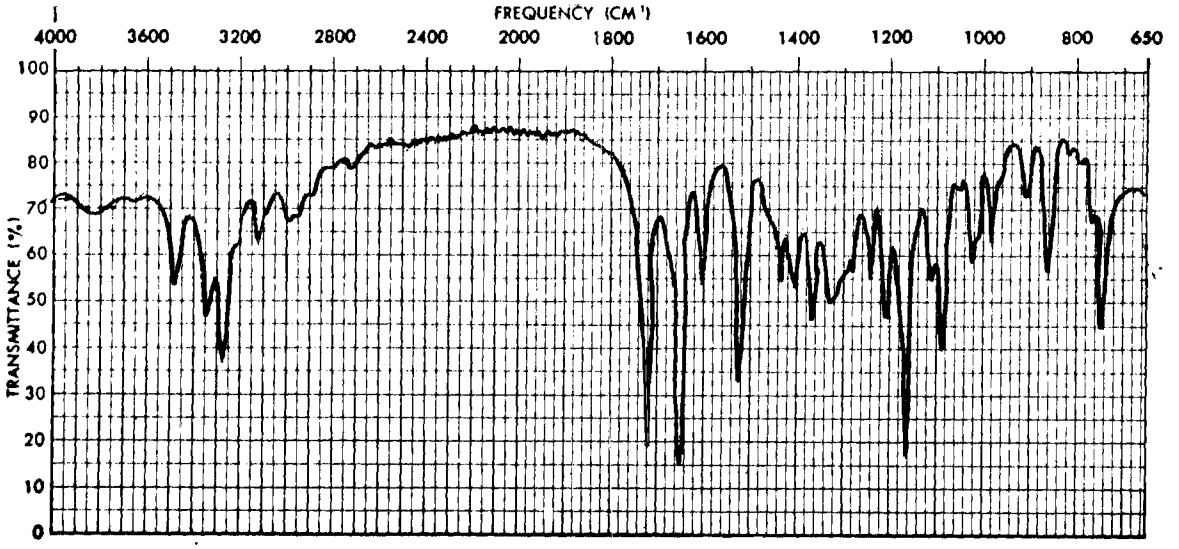


Figure 51. Infrared Spectrum of N-(p-Nitrobenzenesulfonyl)-glutamine Ethyl Ester.

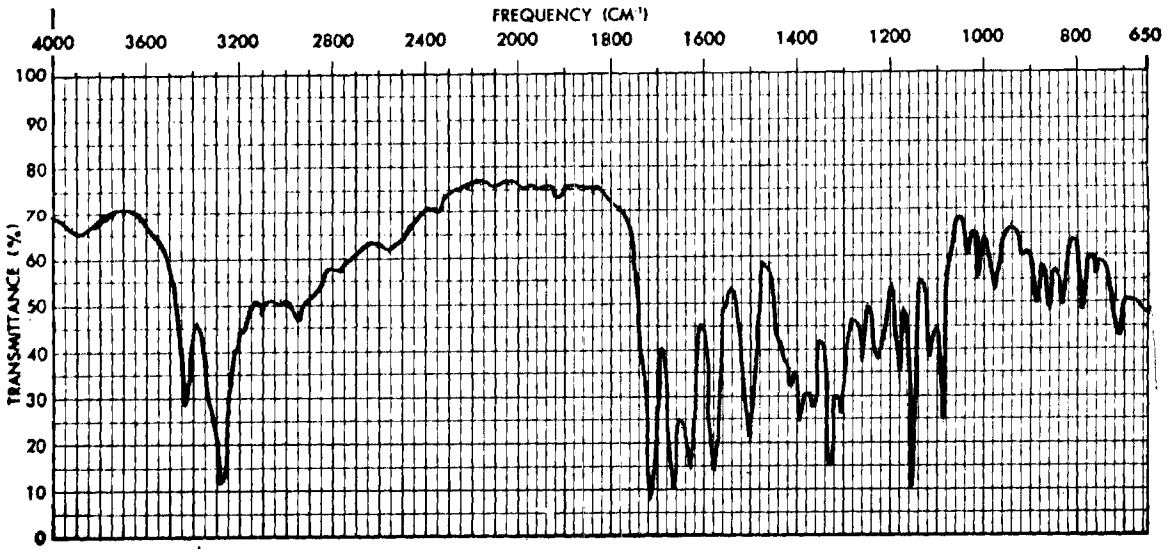


Figure 52. Infrared Spectrum of N^2-(N-Acetylsulfanilyl)-glutamine.

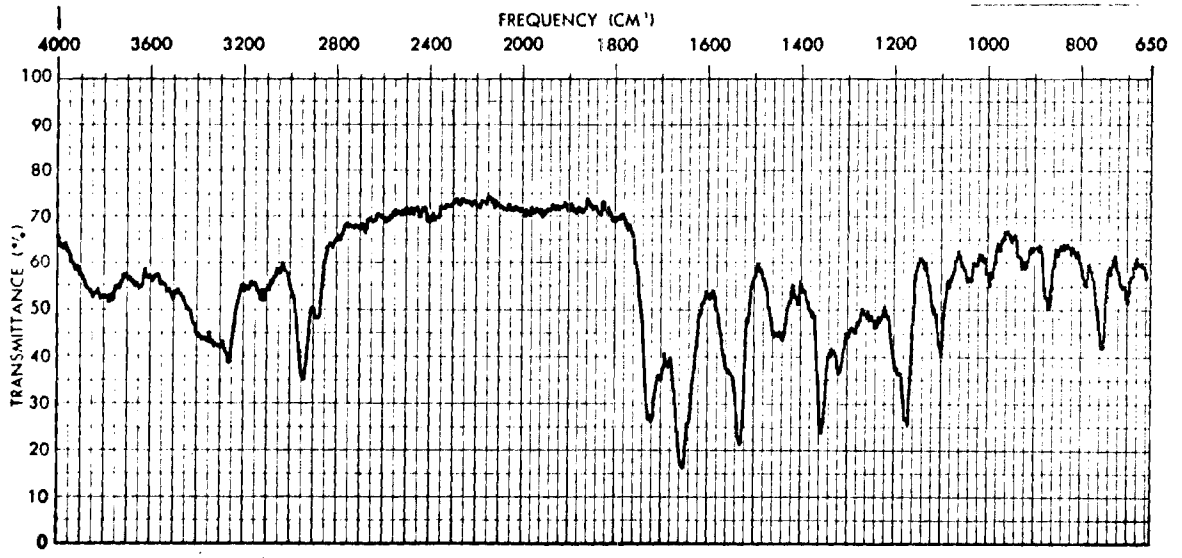


Figure 53. Infrared Spectrum of N^5-Benzyl N^2-(p-Nitrobenzenesulfonyl) glutamine.

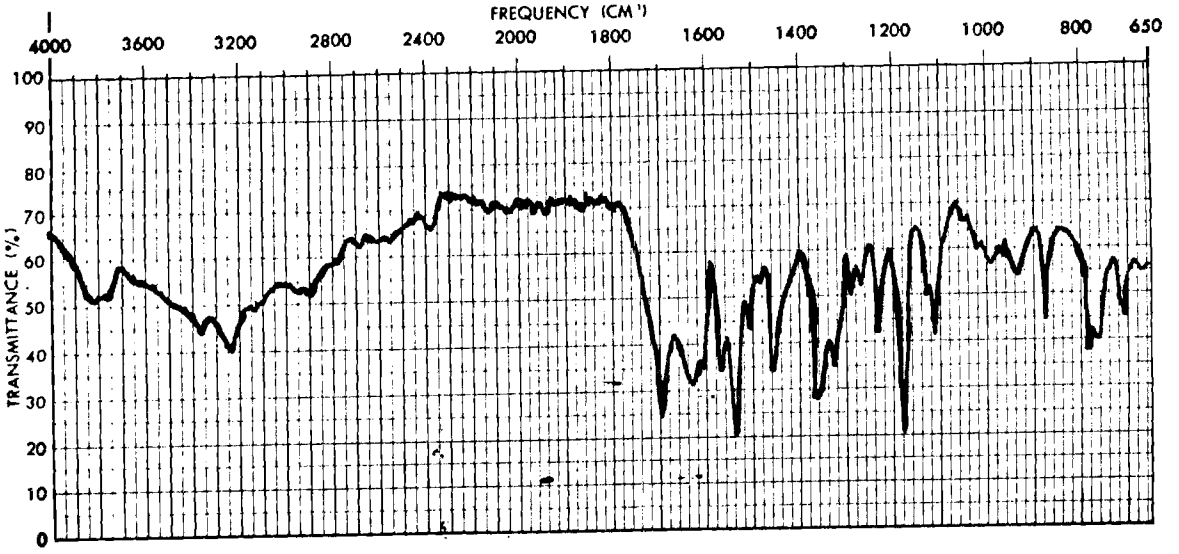


Figure 54. Infrared Spectrum of N^5-Phenyl N^2-(p-Nitrobenzenesulfonyl)-isoglutamine.

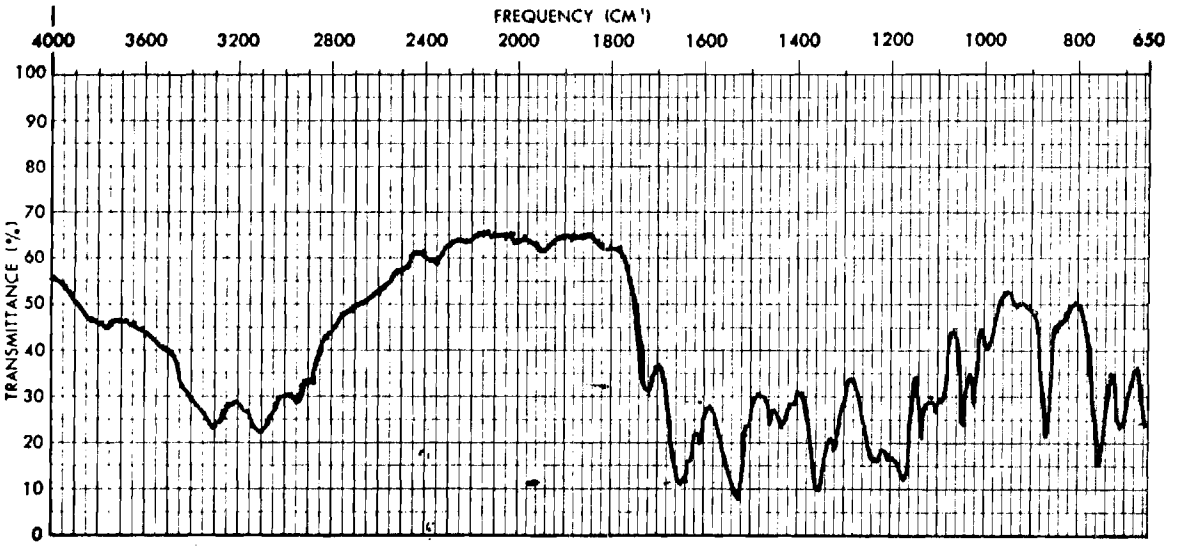


Figure 55. Infrared Spectrum of p-Nitrobenzenesulfonyl-β-glutamic Acid.

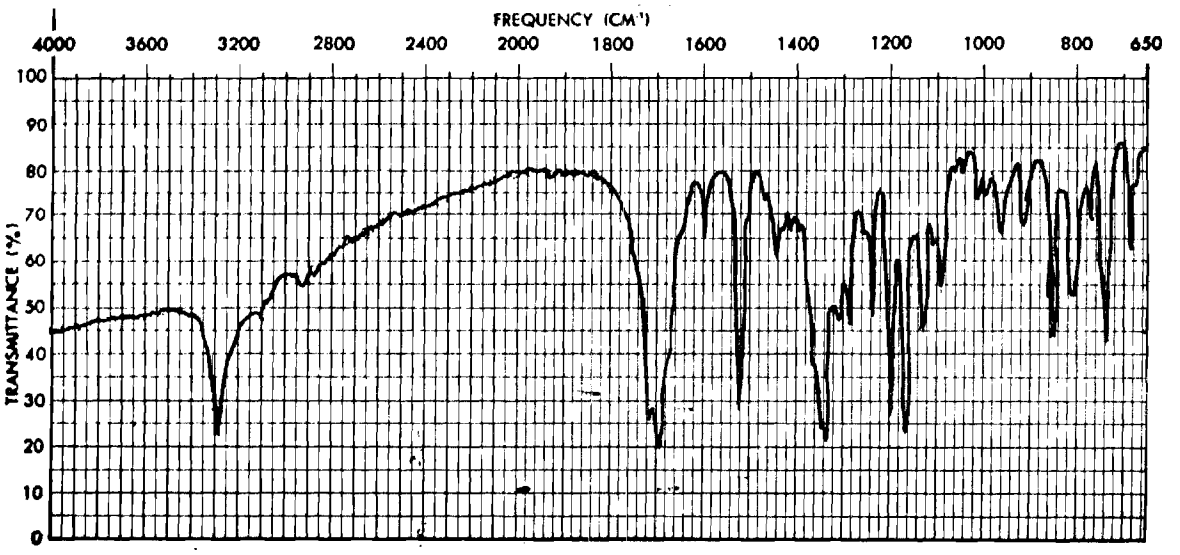


Figure 56. Infrared Spectrum of α-(p-Nitrobenzenesulfonylamido)-glutarimide.

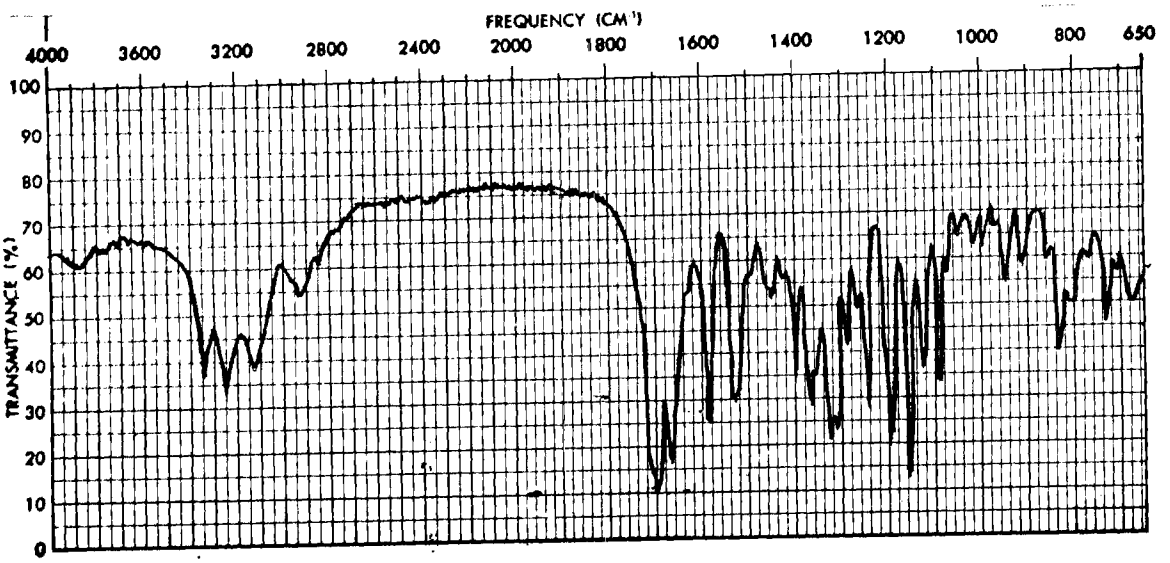


Figure 57. Infrared Spectrum of α-(N-Acetylsulfanilamido)-glutarimide.

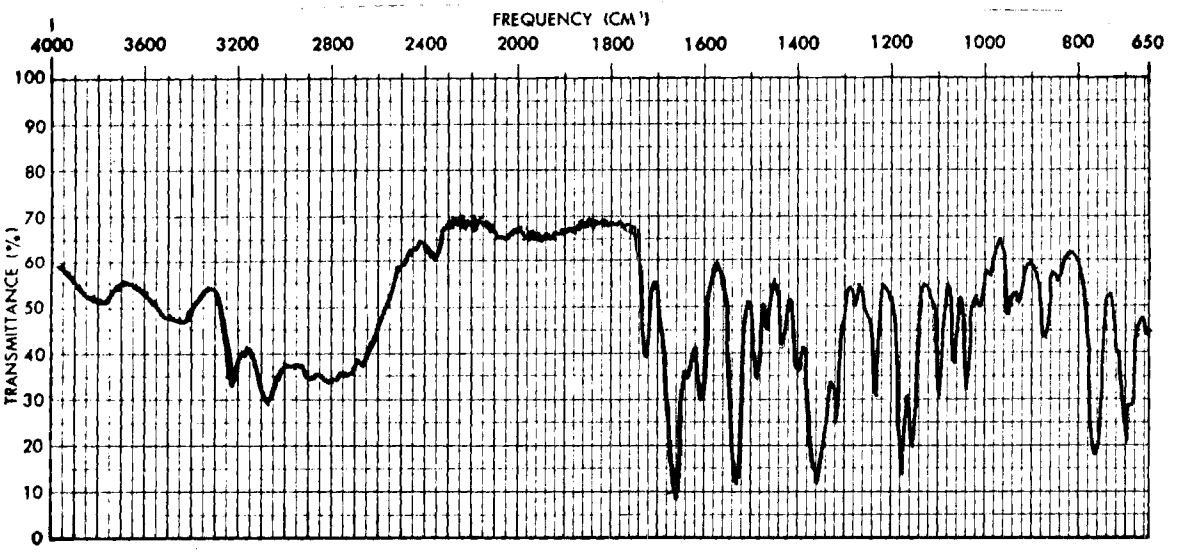


Figure 58. Infrared Spectrum of N-Benzyl β-(p-Nitrobenzenesulfonyl-amido)glutarimide.

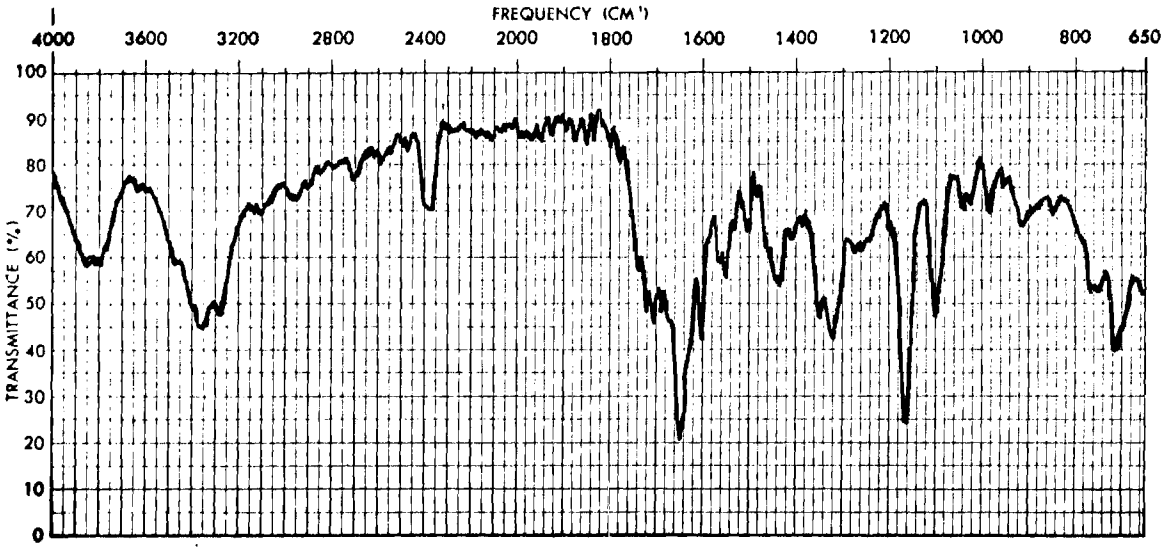


Figure 59. Infrared Spectrum of N-Benzyl Sulfanilylglutamine.

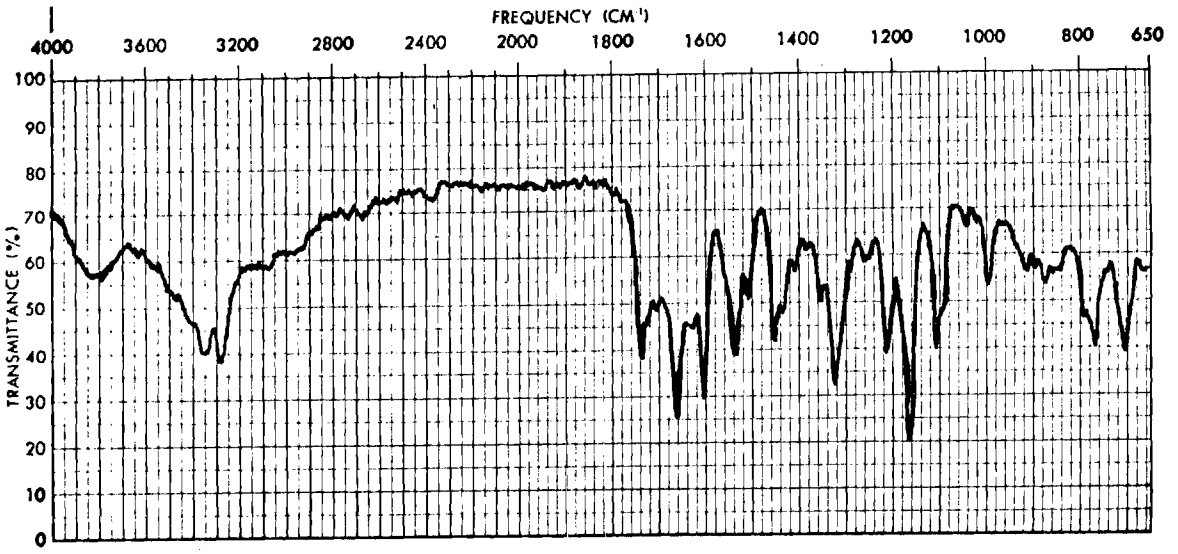


Figure 60. Infrared Spectrum of N-Phenyl Sulfanilylisoglutamine.

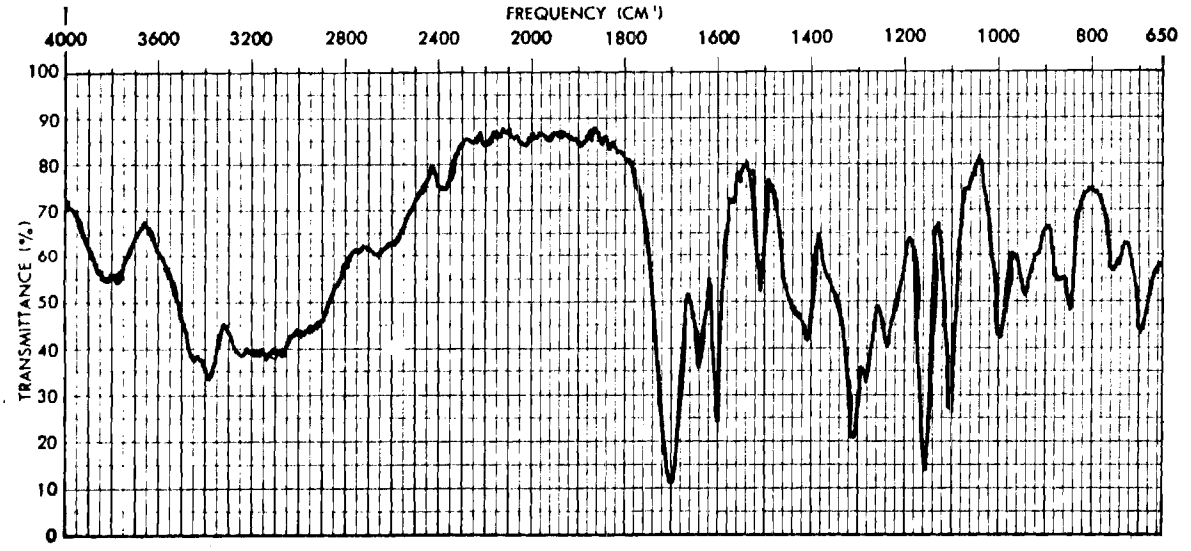


Figure 61. Infrared Spectrum of Sulfanilyl β-Glutamic Acid.

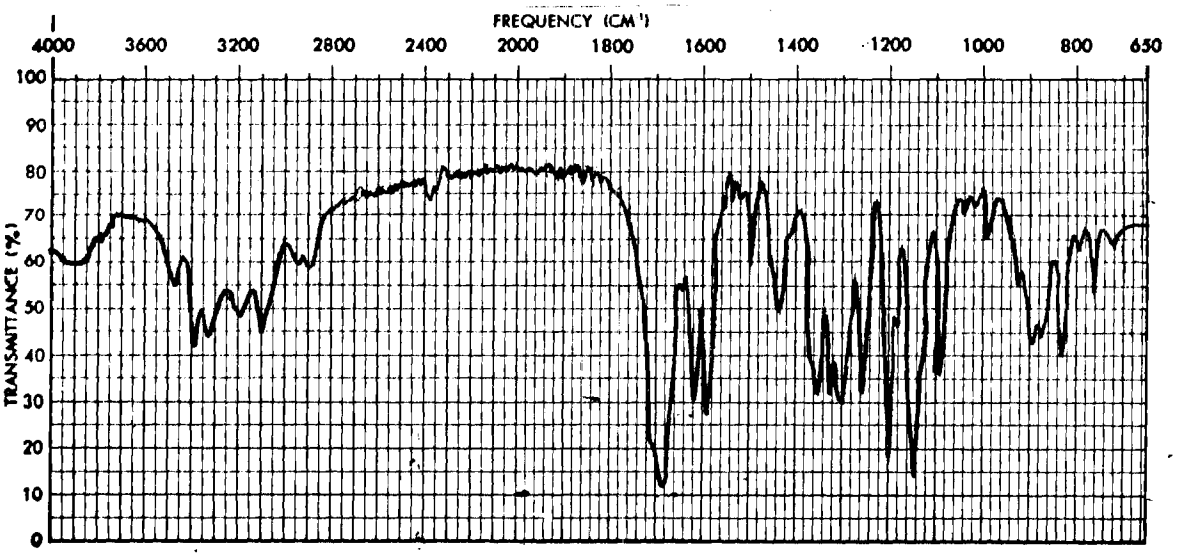


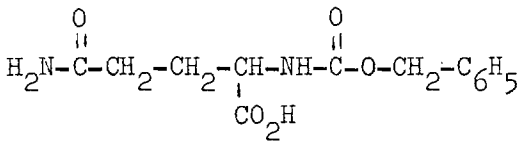
Figure 62. Infrared Spectrum of Sulfanilyl-α-aminoglutarimide.

APPENDIX B

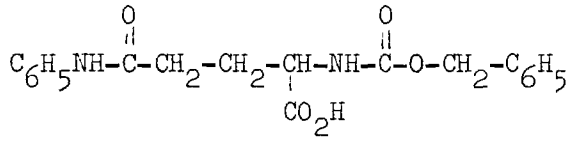
DERIVATIVES OF GLUTAMINE

Derivatives of Glutamine

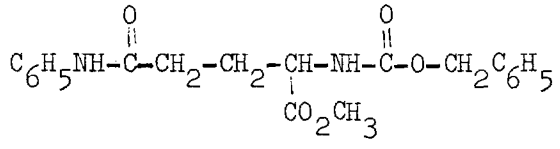
m/e (relative abundance)



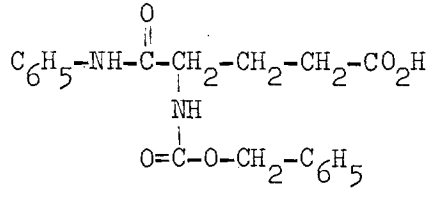
M.W. 280 262(12) 108(100) 107(47) 91(91)
79(35) 77(14) 44(42)



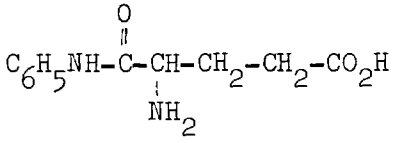
M.W. 370 352(13) 262(20) 244(20) 217(35)
188(13) 174(7) 132(27) 108(67) 107(72)
91(100) 77(53)



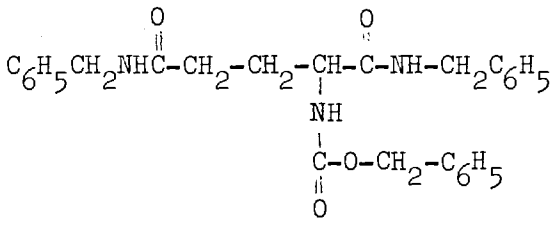
M.W. 384 384(1) 276(38) 261(6) 250(66)
206(52) 188(3) 166(21) 108(21) 170(28)
106(27) 91(100) 84(32)



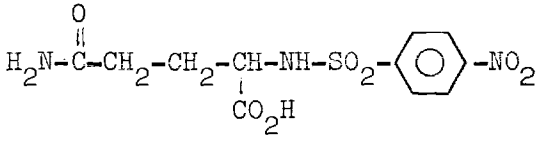
M.W. 356 356(1) 338(6) 248(12) 230(17) 188(19)
119(63) 108(85) 107(75) 93(80) 91(100) 84(61)
79(74) 77(61)



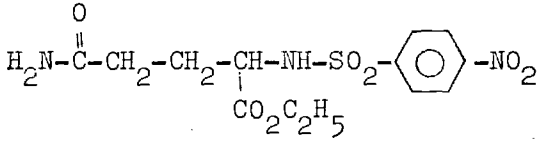
M.W. 222 222(1) 204(62) 102(9) 93(40) 84(100)



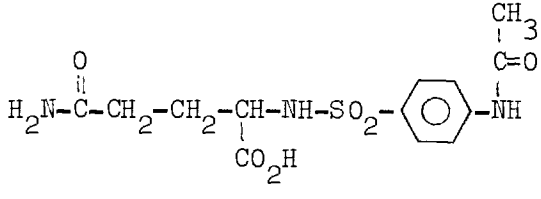
M.W. 459 459(2) 384(21) 352(41) 351(100)
325(14) 244(22) 149(52) 132(26) 108(70)
107(74) 91(66) 79(48) 77(33)



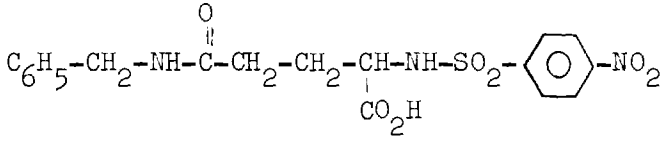
M.W. 331 313(1) 269(100) 250(29) 250(29) 205(63)
186(73) 122(70) 92(16) 75(40) 75(40)



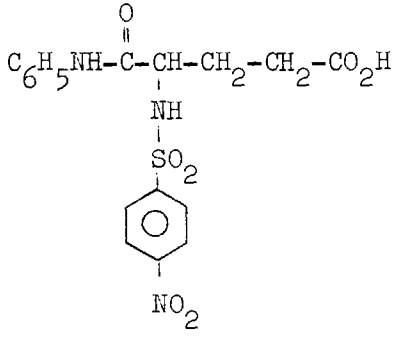
M.W. 359 315(1) 286(3) 278(9) 269(100)
205(11) 186(33) 122(25)



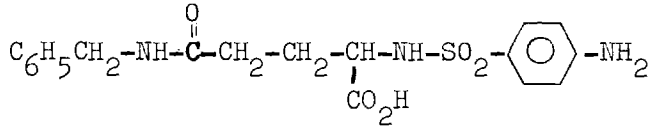
M.W. 343 325(19) 283(19) 262(58) 198(100)
156(69) 134(38) 108(27) 92(50) 84(31)



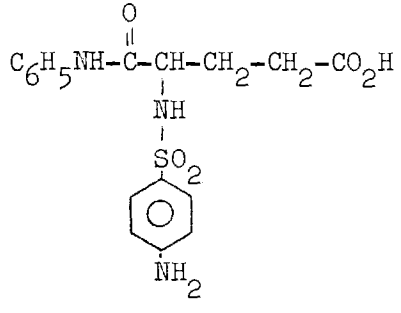
M.W.421 403(10) 269(77) 250(18) 217(72)
205(36) 186(100) 122(68) 107(72) 106(91)
91(71) 84(53)



M.W.407 389(15) 269(100) 250(12) 205(25)
186(54) 122(50) 93(88) 84(27)



M.W.341 373(15) 304(9) 284(9) 239(41)
156(100) 106(74) 92(66) 91(76) 84(86)



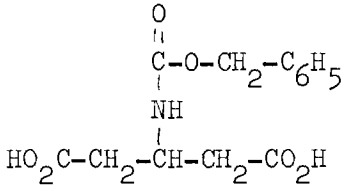
M.W.377 359(14) 248(13) 234(25) 204(42)
156(99) 108(25) 93(42) 92(67) 84(100)

APPENDIX C

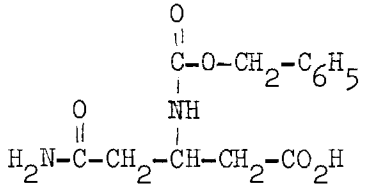
DERIVATIVES OF β-GLUTAMINE

Derivatives of β-Glutamic Acid

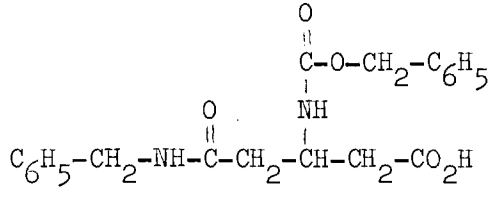
m/e (relative abundance)



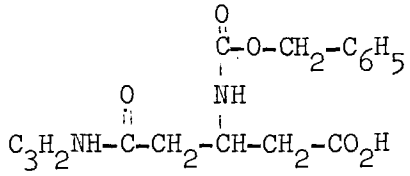
M.W.281 263(1) 232(3) 182(20) 108(100) 107(74) 91(43) 79(85) 77(77)



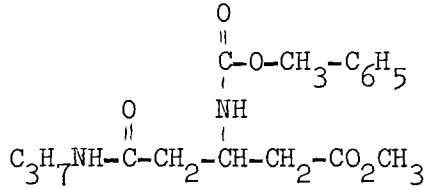
M.W.280 280(1) 253(13) 252(20) 108(95) 107(80) 91(100) 79(46) 77(36) 65(21)



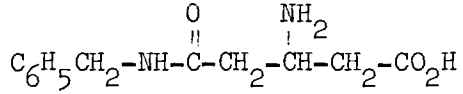
M.W.370 352(1) 261(6) 201(21) 173(11) 108(100) 107(74) 106(58) 91(65) 79(71) 77(68)



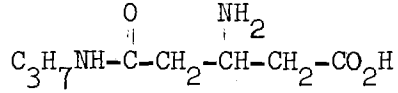
M.W.322 304(4) 263(1) 108(100) 107(65)
91(81) 79(74) 77(74)



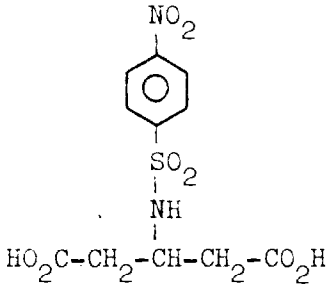
M.W.336 336(47) 305(8) 278(7) 263(4)
229(20) 164(39) 154(20) 142(25) 127(17)
108(33) 107(37) 91(100) 79(23) 77(17)



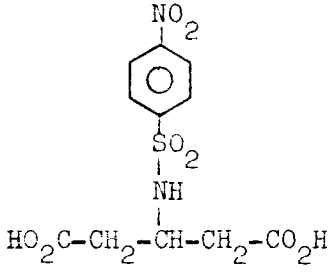
M.W.236 236(55) 190(10) 177(25) 150(43)
149(48) 148(25) 108(48) 106(93) 101(43) 91(100)



M.W.188 188(16) 143(14) 142(16) 129(56)
113(14) 102(37) 101(100) 88(82) 86(63) 70(70)



M.W.332 273(71) 255(60) 229(43) 202(90)
186(100) 146(50) 139(42) 122(90) 102(28) 92(35)



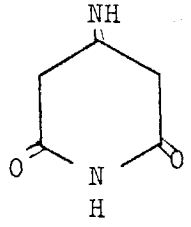
M.W.302 302(2) 243(1) 184(5) 172(19)
156(45) 112(16) 93(45) 92(35) 84(31)

APPENDIX D

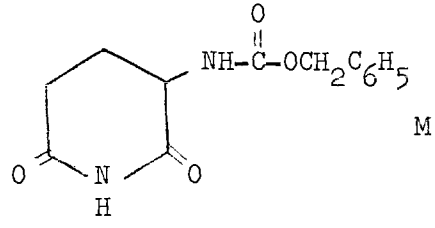
DERIVATIVES OF GLUTARIMIDE

Derivatives of Glutarimide

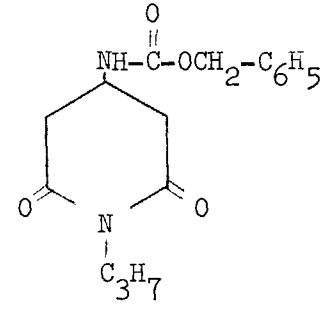
m/e(relative abundance)



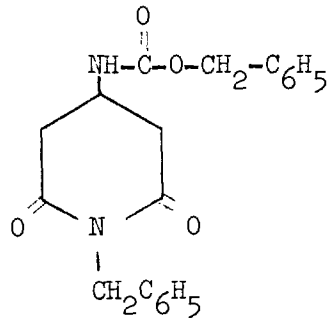
M.W.126 126(100) 83(41) 68(45)
55(32) 54(35)



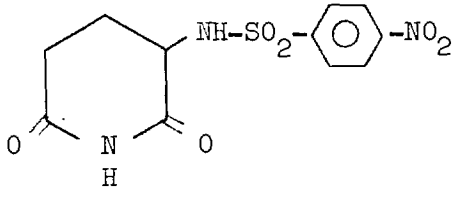
M.W.262 262(6) 108(69) 91(100) 74(10) 77(7)



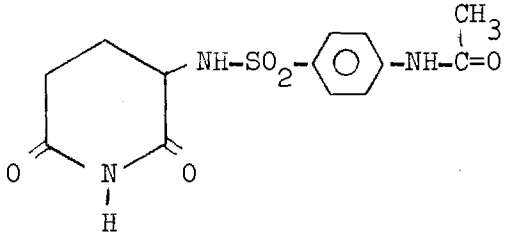
M.W.304 304(35) 154(5) 151(4) 108(61)
91(100) 79(12) 77(9)



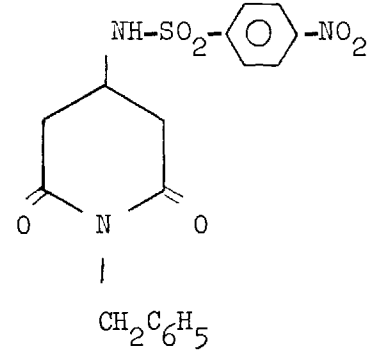
M.W.352 352(7) 252(16) 251(83) 244(100)
180(31) 146(50) 132(51) 108(43) 106(64)
91(59) 79(24) 77(29)



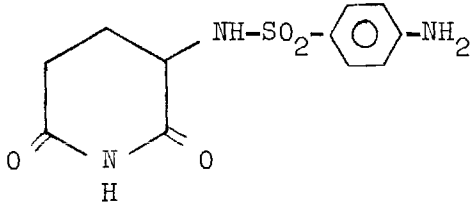
M.W.313 313(6) 209(100) 205(12) 186(41)
149(12) 122(41) 99(31) 92(13) 84(42)



M.W.325 325(81) 292(11) 283(81) 198(57)
156(46) 140(41) 135(41) 134(37) 93(100)



M.W.403 403(20) 202(69) 201(100) 186(33)
173(40) 156(16) 122(36) 106(50) 91(60)



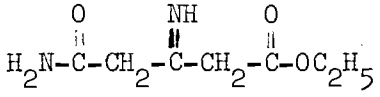
M.W.283 283(100) 198(6) 172(19) 156(99)
108(35) 98(15) 92(73)

APPENDIX E

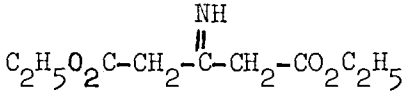
MISCELLANEOUS COMPOUNDS

Miscellaneous Compounds

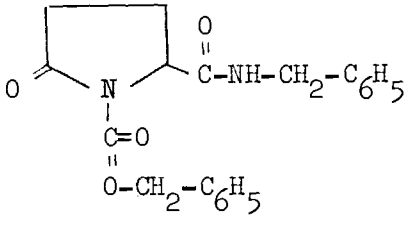
m/e (relative abundance)



M.W.172 172(100) 155(63) 127(96) 110(48)
100(48) 99(42) 98(32) 83(50) 68(43)



M.W.201 201(21) 185(3) 156(25) 129(63)
84(100) 83(38) 57(59)



M.W.352 352(1) 261(3) 244(64) 217(47)
216(100) 133(35) 132(53) 108(75) 107(83)
91(75) 85(83) 79(82) 77(58)

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VITA

John P. Peters was born on December 9, 1944 in Pittsburgh, Pennsylvania to Mandella Tate and Herbert P. Peters. He has one brother, Charles Peters, three years his senior. He attended public schools in Atlanta, Georgia and Marietta, Georgia and was graduated from Sprayberry High School, Marietta, Georgia in 1962. In 1966 he received the Bachelor of Science Degree in Chemistry from Georgia Institute of Technology, Atlanta, Georgia, during which time he was a member of the varsity track and cross-country teams. Upon graduation he enrolled in the Graduate Division, School of Chemistry, at Georgia Institute of Technology. While at Georgia Tech, he held a teaching assistantship in the School of Chemistry for five years.

In August, 1967, he married the former Miss Sheri Elaine Ferguson. They have two sons, Paul Malloy and Clinton Tate.

From February, 1972 until June, 1972 he taught Science and Biology at Arlington High School in Atlanta, Georgia and was also Assistant Track Coach.

Since June, 1972 he was employed as a Research Chemist with Lester Laboratories, Incorporated, Atlanta, Georgia. In Septemper, 1973 he was promoted to Chief Chemist, his present position.